University of Alberta

Assessment of Anemia as a Prognostic Risk Factor in Patients with Congestive Heart Failure.

Justin A. Ezekowitz

Thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science in Medical Sciences – Public Health Sciences

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:elvan

July 23, 2003
Date

Grant me the strength, time and opportunity always to correct what I have acquired, always to extend its domain; for knowledge is immense and the spirit of man can extend indefinitely to enrich itself daily with new requirements. Today he can discover his errors of yesterday and tomorrow he can obtain a new light on what he thinks himself sure of today.

Moses Maimonides,
Dalalat al-Ha'rin (Guide for the Perplexed, 1190 a.d.)

Abstract

Background: Anemia has recently been demonstrated to be a risk factor for poor outcomes in patients with congestive heart failure (CHF).

Methods: A CHF specialty clinic cohort of new patients was analyzed. Multivariate regression and proportional hazards models were used to measure the independent association of different definitions for anemia on mortality using a variety of definitions for anemia.

Results: 1037 patients with CHF were seen in the clinic over a 12-year period. 40% of males and 35% of females were anemic by the WHO definition, which was associated with 1-year and 5-year mortality in males (OR 1.7 [95%CI 1.12 to 2.5], OR 1.76 [95%CI 1.15 to 2.7]) but not females (OR 1.22 [95%CI 0.69 to 2.16], OR 1.15 [95%CI 0.65 to 2.05]).

Conclusions: Anemia is prevalent and predicts mortality in heart failure patients, but the risk is dependent on gender and prediction of mortality risk in this population is complex.

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List of Abbreviations, Nomenclature and Symbols

95%CI = 95% confidence interval
ACE = angiotensin-converting enzyme
ARB = angiotensin receptor blocker
BP = blood pressure
CCB = calcium channel blocker
CDC = Centers for Disease Control
CHF = congestive heart failure
COPD = chronic obstructive pulmonary disease
CrCl = creatinine clearance
DHP = dihydropyridine
EF = ejection fraction
ELITE II = Evaluation of Losartan in the Elderly II
EPO = erythropoietin
Hb = hemoglobin
HbA1c = glycosylated hemoglobin
Hct = hematocrit
HR = hazard ratio
IQR = interquartile range
IV = intravenous
LBBB = left bundle branch block
LVH = left ventricular hypertrophy
MCV = mean corpuscular volume
NYHA = New York Heart Association
OR = odds ratio
SOLVD = Studies of Left Ventricular Dysfunction
TIBC = total iron binding capacity
TGF = tumor growth factor
TNF = tumor necrosis factor
TSH = thyroid stimulating hormone
VO2max = peak oxygen uptake
WHO = World Health Organization

Note: hemoglobin values are presented throughout this manuscript in SI units as g/L. For g/dL values, divide by 10.

Chapter 1: Introduction

1.1 The Problem of Congestive Heart Failure

Congestive heart failure (CHF) is a cause of significant morbidity and mortality and is the most rapidly increasing cardiovascular diagnosis in North America with an overall community prevalence estimated at 0.4% to 2.4%.[1-4] Coronary artery disease is the cause of heart failure in 2/3 of patients, with hypertension, valvular dysfunction, viral myocarditis and idiopathic dilated cardiomyopathy as the etiology for the remainder.[5] Heart failure is a clinical syndrome characterized by specific symptoms and is usually accompanied by a depressed ejection fraction (generally accepted for clinical trials as <40%).[6] Although heart failure has long been considered to be a disorder characterized by depressed left ventricular systolic function, diastolic dysfunction has recently been found to be present in 20% to 40% of patients with symptomatic findings of heart failure and these patients have a mortality rate that is similar to those with systolic heart failure.[4,7] Despite many advances in diagnosis and therapy, symptomatic heart failure carries a poor prognosis with a 30% to 50% mortality rate at 1 year.[1,8] Identification of modifiable risk factors in CHF may lead to the development of novel treatment options for heart failure.

1.1.1 Current Risk Factors and Markers in Congestive Heart Failure

Many prognostic factors in congestive heart failure are recognized to influence morbidity and mortality. Well validated risk factors for short and long-term mortality include demographic factors, such as older age and male gender [9], differing ethnic background[10], co-morbidities such as diabetes[11] and poor renal function[12], and physical examination findings (for example, the presence of a third heart sound and elevated jugular venous pressure)[13]. Biochemical values which predict mortality include decreased serum sodium[14], elevated aldosterone, angiotensin II, and arginine vasopressin[15], elevated brain natriuretic peptide[16] and elevated levels of other neurohormones[17]. Other prognostic risk factors have been explored (genetic, electrocardiographic, echocardiographic and symptomatic findings) and are reviewed elsewhere.[18] Identification of risk factors that can be readily accessed on an individual patient in the clinical setting are needed to direct clinical care, aid prognosis

determinations well as formulate research into novel therapeutic strategies for this complex disease. Hemoglobin, a widely available laboratory test, has only recently been explored as a marker for poor outcomes in congestive heart failure, and is discussed in Section 1.2.

1.1.2 Current Therapeutic Strategies for Congestive Heart Failure

Current therapy for congestive heart failure incorporates a number of strategies in order to enhance the quality of life, improve exercise tolerance, and improve short and long-term survival. In the past two decades, advances in heart failure management have lead to randomized clinical trials of non-pharmacologic interventions (exercise training, care delivery systems), novel medications, electrophysiologic procedures and devices, surgery, and cardiac transplantation.

Angiotensin-converting enzyme (ACE) inhibitors were one of the first medications shown to reduce mortality in congestive heart failure, with a relative risk reduction for the enalapril group (versus placebo) of 40% at 6 months in patients with New York Heart Association (NYHA) Class IV.[19] Since then, other clinical trials and systematic reviews of the 34 randomized controlled trials[20] of ACE inhibitors have confirmed substantial benefits (in the order of 25% to 35% reduction in mortality) in all classes of heart failure, and they are now a mainstay of treatment for systolic left ventricular dysfunction with or without symptoms.[21-26] Beta-blockers are also a cornerstone for the treatment of systolic dysfunction, with systematic reviews of large randomized controlled trials demonstrating consistent benefits in reducing mortality (relative risk reduction 35%), morbidity (relative risk reduction 36%)[27] and improving NYHA class and quality of life[28]. Digoxin has also been shown to reduce hospitalization rates, but no reduction (despite a trend toward significance) in mortality was seen in the largest mortality based trial testing digoxin in congestive heart failure patients with an ejection fraction <45%.[29] Angiotensin-receptor blockers, have not been demonstrated to be of additional benefit for reducing all-cause hospitalizations[30,31], improving quality of life or reducing mortality when used in conjunction with standard medical therapy that includes ACE inhibitors and beta-blockers, but have shown a benefit for reducing all-cause hospitalization for patients intolerant of ACE inhibitors.[32] Aldosterone blockade (using spironolactone or epelrenone) is associated with a relative risk reduction in

mortality of 15% to 30% for patients in NYHA Class III or IV and an ejection fraction <35%[33] and for patients with an ejection fraction <40% and recent myocardial infarction[34].

Novel electrophysiologic therapies such as biventricular pacing have been shown to have a promising role for patients with CHF for the improvement of quality of life, NYHA class and six-minute walk test, but have yet to demonstrate a conclusive mortality benefit.[35] [36]Implantable cardioverter defibrillators provide a substantial mortality benefit for secondary prevention and high-risk primary prevention.[37]

Finally, whereas exercise training of patients with congestive heart failure can result in substantial gains for functional status, this approach has not shown consistent gains and involves regimens that are challenging to implement in an ambulatory care setting.[38,39]

Hence, other novel strategies that result in either a functional improvement, reduced hospitalizations or increased survival in addition to current medical management of congestive heart failure are necessary. The discovery of novel markers that reliably identify risk and track successful therapy in this population are key to developing future effective strategies.

1.2 Anemia in Congestive Heart Failure

1.2.1 Defining Anemia

Definitions of anemia for normal populations have been determined in large population-based surveys by calculating means, standard deviations and outliers for different age, ethnic and gender groups.[40] However, differences in hemoglobin or hematocrit levels may exist between normal populations and patients with congestive heart failure, necessitating exploration of diverse definitions of anemia in the heart failure population. In studies of heart failure and anemia, anemia has been defined variably, including quartiles[41], as a continuous variable[42], or arbitrarily[42-47] reflecting the uncertainty regarding the physiological importance of different levels of hemoglobin or hematocrit as measured in this population. As well, none of the studies have utilized a definition of anemia that incorporates gender despite the accepted lower normal reference values in normal female populations. Definitions for anemia of chronic disease are also variable,

and combine a low hemoglobin or hematocrit and further parameters such as mean corpuscular volume, ferritin, or the presence of iron in bone marrow aspirates.[48,49] There have been no studies of heart failure that have explored the prevalence of anemia of chronic disease using a laboratory-based definition. These uncertainties have prompted the current work.

1.2.2 Evidence of Association from Population Databases

Population databases offer unique insight into heart failure since they represent the entire community of heart failure and patients are unselected and have a "real-world" distribution of co-morbidities. We have recently demonstrated a 17% prevalence of anemia in an inception cohort of 12,065 unselected heart failure patients in Alberta, 58% of whom had anemia of chronic disease.[50] The 1-year and 5-year mortality of patients with new-onset CHF and anemia was 38% and 59%, respectively, versus 27% and 50% in those without anemia. Even after adjustment for important comorbidities and known prognostic risk factors, the 1-year mortality hazard ratio was 1.36 (95%CI 1.24 to 1.46). The association of anemia with mortality in heart failure was even more marked in the youngest and healthiest subgroup (odds ratio 2.4 [1.2 to 4.6]). Heart failure patients with anemia of chronic disease (compared to heart failure patients without anemia) were at increased risk for 1-year mortality even after adjustment in a Cox regression model (HR 1.36 [1.23 to 1.50]).(See Appendix A for a reprint of this manuscript completed as part of my thesis)

Two other recent analyses of the United States Medicare population (over 65 years of age) have demonstrated similar poor outcomes for heart failure patients with anemia.[42,45] Both of these studies used data of patients admitted to hospital with a primary diagnosis of heart failure, and had similar results: a decrease in hematocrit is associated with an increase in mortality. Importantly, patients with a lower hematocrit were at higher risk for recurrent hospitalization within 1-year (HR 1.02 per 1% lower hematocrit [95%CI 1.01 to 1.03].[42] Kosiborod and colleagues attempted to further clarify the cause of anemia by collecting white blood cell counts and platelet counts.[42] However, this failed to provide any useful information as to the cause and outcomes of these patients, mainly because these laboratory markers have little bearing on the cause of

anemia other than malignancy or rare bone marrow disorders; a thorough search of the diagnostic codes would have provided this information.

1.2.3 Evidence of Association from Clinical Trials

Clinical trials provide a high level of evidence for benefit or harm of novel therapies, and also contribute a wealth of clinical and laboratory data on thousands of patients with heart failure. In a highly select clinical trial population of 6563 patients in the Studies of Left Ventricular Dysfunction (SOLVD) study, 4.4% of the cohort had a hematocrit <35%, and each 1% drop in hematocrit was associated with a higher mortality (HR 1.03 [95%CI 1.02 to 1.04]).[51] Anemia was defined arbitrarily by a hematocrit of <35%; however, this trial had inclusion (ejection fraction <35%, age 21 thru 80) and exclusion (creatinine > 2.5 mg/dL) criteria that limit its relevance to the general population of heart failure patients. In a preliminary analysis of the Evaluation of Losartan In The Elderly (ELITE II) trial, Anker and colleagues demonstrated a non-linear relationship of hemoglobin to survival, as those patients with a hemoglobin of 14.5 to 15.4 g/dL had the highest 2-year survival (85%) when compared to those above (75%, Hb >15.4 g/dL) or below (75%, Hb <12.5 g/dL) this range.[44] Both of these trials had important inclusion or exclusion criteria that limits the applicability to the general heart failure population when exploring the relationship between anemia, heart failure and survival.

1.2.4 Evidence of Association from Specialty Clinics

Specialty clinics in heart failure offer a unique opportunity to assess novel risk factors for mortality, since there is systematic collection of clinical data together with detailed assessments by individuals trained in the management of congestive heart failure and extensive use of evidence-based medications. Horwich and colleagues demonstrated in a specialty heart failure/transplant clinic of 1061 patients with New York Heart Association Class III or IV symptoms that patients in the lowest quartile of hemoglobin (<12.3 g/dl) had a two-fold increase in mortality or need for urgent transplantation at 1-year.[52] This study however, represents a young (mean age 52 years), predominantly male (77%) population, excluded patients with an ejection fraction >40% and were unable to distinguish the etiology of anemia; the results were unfortunately not adjusted for all-

important covariates (including medications). Another small (n=142) study by Silverberg and colleagues showed the prevalence of anemia varies with the severity of heart failure, and ranges from 9.1% to 79.1%.[46] The same research group also showed that treatment with recombinant subcutaneous erythropoetin (EPO) and intravenous (IV) iron improved morbidity in a small, open-label observational study of 32 patients with both anemia and CHF.[47] These studies were the first to indicate that anemia may be important within a CHF population, and potentially correctable. However, interpretation of this data is limited by either the insufficient number of patients available for analysis[46], short follow-up intervals[41,46] or inability to adjust for important covariates.[41]

1.3 Pathophysiologic Rationale for Anemia Modulating Outcomes in Congestive Heart Failure

The above epidemiological heart failure data suggest that anemia is linked to mortality, but are unable to elucidate the pathophysiologic mechanisms by which these are connected. Peak oxygen uptake (VO_{2max}), a specific measure of oxygen carrying capacity used in chronic heart failure patients and for selection of cardiac transplant patients, has been well validated to be a significant predictor of mortality in patients with congestive heart failure.[53] Patients with a VO_{2max} of <14mls/kg/min had an annual mortality rate of 30% whereas those >14 mls/kg/min had a 6% annual mortality rate; this value is widely used to aid selection of candidates for cardiac transplant.[54] The relationship between hemoglobin and VO_{2max} has recently been explored in a recent cross-sectional exercise study, demonstrating a strong relationship with hemoglobin levels.[55] Kalra et al. showed that VO_{2max} was lower in those with a hemoglobin < 13 g/dL versus those above 13 g/dL (16.4 vs. 20.6 ml/kg/min, p=0.0001). Furthermore, the relationship between hemoglobin and maximum oxygen consumption was linear below 13 g/dL (r=0.41, p=0.014). Oxygen delivery to myocardium and other tissues is dependent on two main factors: (1) flow of blood through the major arteries supplying the tissue, and (2) the content of oxygen in the blood, primarily determined by hemoglobin concentration and structure. Whereas reduced arterial oxygenation increases cardiac output in healthy individuals, this compensatory mechanism is compromised in those with moderate to severe CHF, coronary stenosis, or advanced age thereby contributing to poorer outcomes in patients with CHF.[56-58]

The basic pathophysiologic mechanisms that cause anemia in heart failure are unknown and complex, likely modulated in part by many inflammatory mediators, renal function, erythropoietin function, the renin-angiotensin axis and medications used for the treatment of heart failure.[59-61] For example, tumor-necrosis-factor-α is known to be elevated in CHF[62] and has been implicated in anemia of chronic disease.[63-65] Interferon-γ (elevated in heart failure) directly inhibits erythroid progenitor cells capacity for erythropoesis; this may be mediated in part by nitric oxide which blocks heme biosynthesis.[61,66] Both these examples demonstrate some of the complexity in heart failure signaling and the interaction between heart failure and hematopoetic processes. Furthermore, many patients with heart failure are on anti-platelet (e.g. aspirin, clopidogrel) and anti-coagulant (e.g. warfarin) medications which increase the risk of gastrointestinal blood loss. Angiotensin-converting enzyme inhibitors, now a requisite component of therapy for CHF have also been associated with anemia in human and experimental heart failure models.[67-69] Both of these therapeutic potential etiologic factors underscore the necessity to explore a representative heart failure population that includes detailed medication data to permit appropriate multivariate analysis so as to establish associations of causality.

1.5 Improvements over Previous Work

The effect of anemia mortality in a large cohort of heart failure patients within a specialty clinic, after adjustment for important covariates including medication use, is not known. Although previous work has examined the prevalence and outcomes of CHF patients with anemia in a specialty clinic, the robustness of these analysis are limited by insufficient patient numbers or inadequate adjustment for important covariates, selection bias and non-standard definitions for anemia. Furthermore, both the prevalence of anemia of chronic disease in a specialty heart failure clinic as well as the relationship it has to relevant clinical, laboratory and therapeutic findings is unclear. Finally, the relationship between anemia and gender, etiology (ischemic or non-ischemic) of CHF, and type (diastolic or systolic) of CHF is not understood from the current literature.

Chapter 2: Objectives, Rationale and Hypotheses

1. To determine the prevalence of anemia of chronic disease in congestive heart failure patients using a laboratory-based definition.

   Rationale: Anemia of chronic disease is the result of multiple chronic pathophysiologic processes related to disease severity. Previous work has used a clinical definition for anemia of chronic disease and applied this to a heart failure population; we will use a validated laboratory definition of anemia of chronic disease to determine the relationship between anemia of chronic disease and mortality in this population.

   Hypothesis: Anemia of chronic disease will form the majority of causes for anemia in the heart failure population.

2. To determine the relationship between anemia and survival in congestive heart failure patients after adjusting for other known prognostic factors and therapies.

   Rationale: Congestive heart failure has many risk factors and adjustment for these must be adequately done to ensure that anemia is an independent predictor of mortality.

   Hypothesis: The presence of anemia will predict a higher mortality in congestive heart failure patients, even after adjustment for known prognostic factors and therapies.

3. To determine the demographic, clinical or biochemical features that are associated with the presence of anemia in a CHF population; specifically, to define the relationship of gender, etiology of heart failure (ischemic versus non-ischemic) and type of heart failure (diastolic versus systolic) to anemia.

   Rationale: Previous work has not adequately examined the relationship that etiology of heart failure (ischemic versus non-ischemic) may have with anemia; non-ischemic heart failure patients represent a sub-group of heart failure with a different prognosis. Female heart failure patients also have a different prognosis than males, and normal populations have demonstrated

differing normal ranges of hemoglobin between males and females. Furthermore, few patients in previous studies had diastolic dysfunction.

Hypothesis: Anemia will be equally common in those with ischemic or non-ischemic backgrounds; anemia will be equally common in those with systolic or diastolic dysfunction; and more females will have anemia than males in this population.

Chapter 3: Methods

3.1 Study Population

Data was collected prospectively on 1151 adult patients referred to the University of Alberta Hospital Heart Function Clinic for evaluation and management of heart failure between September 1989 and July 2001. A full description of this clinic has been published,[70] but in brief, this clinic is multidisciplinary (includes physicians, pharmacists, dieticians and nurse practitioners) and evaluates patients referred by family physicians, internists, or cardiologists for assessment and management of chronic heart failure. Management of each patient was at the discretion of the attending clinic physician, and although maximal current medical therapy was stressed at each visit, no specific protocols or critical pathways were used during the period of this study. Each patient was examined by a Heart Function Clinic physician at their first visit and the 1037 confirmed to have congestive heart failure (on the basis of the Framingham Heart Study criteria, Table 1)[71] were included in this study. Patients were followed-up (in hospital, at the clinic or via phone follow-up) at varying intervals depending on clinical status.

Table 1. Framingham Criteria for the Diagnosis of Congestive Heart Failure

Major Criteria	**Minor Criteria**
Paroxysmal nocturnal dyspnea	Bilateral ankle edema
Rales	Nocturnal cough
Radiographic cardiomegaly	Dyspnea on exertion
Acute pulmonary edema	Hepatomegaly
S_3 gallop	Pleural effusion
Increased venous pressure (>16 cm H_2O)	Vital capacity reduced $1/3^{rd}$ from normal
Positive hepatojugular reflux	Tachycardia (120 ≥bpm)
Major or Minor	
Weight loss ≥4.5kg over 5 days treatment	

The diagnosis of congestive heart failure requires that 2 major or one major and 2 minor criteria be present concurrently. Minor criteria are accepted only if they cannot be attributed to another medical condition.

3.2 Study Variables

Demographic, clinical, medications, laboratory, and imaging data were collected prospectively at the first visit and each subsequent visit via a structured clinical assessment, and entered into a computerized database; the variables collected are outlined in Tables 2 and 3 and a sample data collection form is in Appendix B. Objective assessments (by echocardiography, radionuclide or contrast ventriculography) of LVEF were obtained in all patients within 3 months of initial presentation to the clinic. Although the precision of these methods differs, each method has been shown to confer similar prognostic information.[72] Patients were defined as having systolic dysfunction if their LVEF was <45%. If patients had a baseline LVEF of 45% to 50%, they were classified as having systolic dysfunction unless the echocardiogram indicated that the predominant problem was in ventricular diastolic relaxation (in which case they were classified as having diastolic dysfunction). If patients had a baseline LVEF >50%, they were classified as having diastolic dysfunction. The causes of heart failure were classified as ischemic (history of myocardial infarction, coronary revascularization, angiographically documented stenosis >75% in at least one coronary artery, or focal areas of akinetic myocardium detected on echocardiography, radionuclide stress testing, or contrast ventriculography) or non-ischemic by the Heart Function Clinic physician. Atrial arrhythmias included atrial fibrillation, atrial flutter, or multifocal atrial tachycardia. Ventricular arrhythmias included a history of cardiac arrest, documented ventricular tachycardia, ventricular fibrillation, or frequent premature ventricular complexes (>5/minute) on 24 hour Holter monitor. The diagnosis of left ventricular hypertrophy was determined based on the electrocardiogram using the Romhilt-Estes criteria. Estimated creatinine clearance (CrCl) was calculated by the Cockroft-Gault formula, and creatinine clearance was divided into normal (CrCl > 90 ml/min), mild renal impairment (CrCl 60 to 89 ml/min), moderate renal impairment (30 to 59 ml/min) and severe renal impairment (<30 ml/min).[73]

3.3 Definitions of Anemia

Anemia was *a priori* defined by: (1) quartiles of hemoglobin, with the lowest quartile representing anemia; (2) Centers for Disease Control (CDC) definitions for men (<135 g/L) and women (<120 g/L),[74] which are based on the 5th percentile from the 3rd

National Health and Nutrition Examination Survey; and (3) the World Health Organization definition of anemia for men (<130 g/L) and women (<120 g/L).[75] To establish an accepted criteria for a normal ferritin for defining anemia of chronic disease, a survey was done of a General Internal Medicine Division at the University of Alberta, allowing for three values of ferritin selected from the relevant literature: (1) >18 μg/L (2) >45 μg/L and (3) >100 μg/L. Of the respondents, 86% selected ferritin >45 μg/L as an accepted definition. We defined anemia of chronic disease using the WHO criteria for anemia in combination with a normal ferritin (>45 μg/L) and a mean corpuscular volume within the normal range (80 fL to 100 fL).[76,77] Information on total iron binding capacity, serum iron, saturation index, and thyroid stimulating hormone (TSH), where available, is presented for descriptive purposes.

3.4 Ascertainment of Follow-up

Mortality data was ascertained by review of the Alberta Vital Statistics Registry, death certificates, or review of medical records as of August 2002; follow-up was available for all patients for the ascertainment of vital status. The median time of follow-up was 926 days (interquartile range 318 to 1834 days).

3.5 Data Collection and Assurance

All variables were entered into a computer database and data collation, and quality assurance was carried out at the Epidemiology Coordinating and Research Center, Division of Cardiology, University of Alberta. Since hemoglobin data was prospectively collected, but not entered into the main database for 97% of the individuals in the database, a search of local electronic databases was completed by a trained health professional using standardized abstraction methods. The hemoglobin, ferritin, mean corpuscular volume, and other biochemical indices were matched to the time of baseline visit. After completion of the database update, 791 (76%) individuals had useable data for hemoglobin, 118 (11%) for ferritin, and 658 (63%) for mean corpuscular volume (MCV). For the definition of anemia of chronic disease, 118 patients had data available. Data for other variables was complete with the exception of sodium (98% complete), potassium (99%) and creatinine (99%); other baseline clinical variables were complete. Patients with missing data for hemoglobin were excluded from analysis.

3.6 Statistical Analysis

The baseline characteristics of those with or without anemia were compared using the Chi-square test for dichotomous variables and Student's t-test or Wilcoxon rank sum test for continuous variables. The unadjusted association between levels of hemoglobin (in quartiles as well as the definitions defined above) and mortality was done by Chi-square test. Unadjusted survival curves were generated by the Kaplan-Meier method and compared with the Mantel-Haenszel log-rank test. To calculate 1-year, 2-year and 5-year mortality rates from the survival curves, the technique of comparing two survival curves for grouped data was used.[78] To adjust for differences in baseline clinical characteristics and concomitant conditions/medications in determining the predictors of 1-year mortality, multiple logistic regression analysis with the purposeful selection technique was done, selecting all clinically important variables and other pre-specified factors with $p<0.25$ on bivariate analyses. Multiple logistic regression analyses were run to determine which factors were associated with mortality and statistical significance was accepted at $p<0.05$, and all first-order interactions were tested. Logistic regression models were done on the entire cohort and a stratified analysis was done for gender. Cox proportional hazards analyses were done to determine the association of anemia with overall mortality (over the entire follow-up period), adjusted for age, gender, NYHA class, concomitant medication use, and any other variables which significantly differed between patients with or without anemia or predicted mortality in the multivariate model. The proportional hazards assumption was checked using a log minus log plot and the assumptions were met for variables in the final model.

Hemoglobin was run as a continuous variable and divided into quartiles for the logistic regression model. Sodium, creatinine, systolic blood pressure, diastolic blood pressure, heart rate, weight, and ejection fraction were treated as continuous variables as well as run as categorical variables (defined by the median value for the cohort). Creatinine clearance was included as a continuous variable as well as a categorical variable of normal, mild, moderate, and severe renal insufficiency as defined above. Age was run as a continuous variable in the analysis. Continuous variables were checked for linearity. All analyses were performed with SPSS® statistical software package (version 11.5).

3.7 Ethics

Approval of the Research Ethics Board of the University of Alberta was obtained before conducting the study (Appendix C).

Chapter 4: Results

4.1 Baseline Characteristics of All Patients

1037 patients met the Framingham criteria for congestive heart failure;[71] 34% of patients were female and the median age of all patients was 66 years (standard deviation (SD) 14). Ischemic cardiomyopathy was present in 66% of patients, 72% had an ejection fraction <50%, and 76% were in New York Heart Association (NYHA) Class II or III at their first visit; 37% of patients died during follow-up. The baseline characteristics of the overall cohort are summarized in Table 2, stratified by mortality.

Table 2. Baseline Characteristics of 1037 Patients with Heart Failure.

	Dead (n=383)	Alive (n=654)	P
Demographic			
Age (years)	70 (13)	65 (15)	<0.001
Male (%)	70	63	0.036
Cardiovascular History (%)			
NYHA Class			
I	7	14	
II	31	41	<0.001
III	45	39	
IV	6	7	
Ischemic Etiology	73	61	<0.001
Diabetes Mellitus	26	24	0.336
Dyslipidemia	6	13	0.001
Clinical Variables			
Ejection Fraction	32 (14)	34 (15)	0.039
Weight (kg)	76 (18)	78 (18)	0.029
Heart Rate (bpm)	79 (16)	79 (15)	0.893
Systolic Blood Pressure (mmHg)	120 (24)	124 (25)	0.005
Diastolic Blood Pressure (mmHg)	72 (12)	75 (13)	<0.001
Concurrent Medications (%)			
ACE Inhibitors	82	86	0.09
Beta-Blockers	31	54	<0.001
Warfarin	46	43	0.478
Aspirin	67	65	0.586
Digoxin	70	62	0.014
Spironolactone	1	20	<0.001
Vasodilators	4	16	<0.001
Laboratory Values			
Hemoglobin (g/L)	129 (19)	132 (18)	0.028
Sodium (mmol/L)	138 (4)	139 (3)	0.184
Creatinine (mmol/L)	142 (81)	118 (60)	<0.001
Creatinine Clearance (ml/min)	53 (30)	67 (36)	<0.001

Values are presented as percents or means (standard deviation) ACE = angiotensin converting enzyme; NYHA = New York Heart Association.

4.2 Baseline Characteristics of Patients with Hemoglobin Measurement

Patients who had a hemoglobin value in the database (n= 791) were similar in all respects, i.e. age, gender, ischemic history, NYHA Class, systolic dysfunction, and ejection fraction to those that did not have a hemoglobin value in the database (n=246) and are thus considered representative of the overall clinic population.(Appendix D) The baseline characteristics of patients with a hemoglobin value are summarized in Tables 2 and 3, by quartiles of hemoglobin. Compared to patients above the median hemoglobin value of 131 g/dl, those below the median were older (OR 1.02 per year [1.01 to 1.03]), more likely to be female (OR 2.44 [1.80 to 3.29]), in NYHA Class III/IV (OR 1.72 [1.29 to 2.29]), have ischemic etiology of their CHF (OR 1.50 [1.11 to 2.02]), a higher ejection fraction (OR 1.02 per % increase in EF [1.01 to 1.03]), have received a pacemaker (OR 1.87 [1.05 to 3.31]), have a lower body weight (OR 0.98 per kilogram [0.97 to 0.99]), and lower diastolic blood pressure (OR 0.97 per mmHg [0.96 to 0.98]),.(Table 2) Those above the median were more likely to be on ACE inhibitors (OR 1.71 [1.17 to 2.49]) and less likely to be on a dihydropyridine CCB (OR 1.86 [1.26 to 2.74]), but no differences were seen with aspirin, warfarin or other concomitant medications. Those below the median were also more likely to have a lower sodium (OR 0.95 per mmol/L [0.91 to 0.99]), creatinine (OR 1.01 per mmol/L [1.01 to 1.01]), and creatinine clearance (OR 0.95 per ml/min [0.91 to 0.99]), but no differences were noted in ferritin, TIBC, saturation index, MCV or TSH.(Table 4)

Table 3. Baseline Characteristics of 791 Heart Failure Patients by Quartiles of Hemoglobin.

	Quartile 1 Hemoglobin <119 g/L (n=197)	Quartile 2 Hemoglobin 119 to 131 g/L (n=202)	Quartile 3 Hemoglobin 132 to 144 g/L (n=202)	Quartile 4 Hemoglobin >144 g/L (n=194)	p *	p **
Demographic						
Age (years)	68 (15)	70 (13)	68 (13)	63 (15)	<0.001	0.002
Male (%)	54	55	67	85	<0.001	<0.001
Cardiovascular History (%)						
NYHA Class						
I	6	6	10	14		
II	33	32	39	42	0.012	0.002
III	46	49	40	36		
IV	15	13	12	8		
Ischemic Etiology	50	63	51	46	<0.025	0.008
Hypertension	36	34	29	35	0.582	0.448
Ejection Fraction	37 (14)	35 (15)	32 (15)	31 (14)	<0.001	<0.001
Diastolic Dysfunction	19	14	14	11	0.190	0.094
Ventricular Arrhythmias	19	20	23	16	0.375	0.565
Atrial Arrhythmias	27	31	37	32	0.171	0.073
Pacemaker	9	8	6	4	0.144	0.030
Concomitant Conditions (%)						
COPD	13	11	10	12	0.757	0.517
Diabetes Mellitus	31	21	22	21	0.050	0.081
Dyslipidemia	9	9	9	11	0.921	0.920
Physical Findings						
Weight (kg)	74 (18)	71 (16)	78 (18)	83 (18)	<0.001	<0.001
Heart Rate (bpm)	79 (15)	78 (16)	79 (16)	80 (15)	0.631	0.728
Systolic BP (mmHg)	122 (26)	118 (24)	122 (25)	124 (23)	0.046	0.059
Diastolic BP (mmHg)	70 (14)	70 (11)	75 (13)	77 (12)	<0.001	<0.001
Edema Present (%)	32	25	26	23	0.181	0.130
Electrocardiogram (%)						
LBBB	24	30	31	29	0.411	0.327
LVH	27	32	25	35	0.145	0.996
Concurrent Medications (%)						
ACE Inhibitors	76	82	86	86	0.008	0.005
ARB	4	4	6	5	0.812	0.377
Beta-Blockers	38	45	48	47	0.139	0.083
CCB DHP	19	21	15	8	0.004	0.002
CCB Non-DHP	8	9	10	7	0.708	0.719
Warfarin	39	47	45	51	0.109	0.316
Aspirin	70	70	70	59	0.033	0.244
Aspirin or warfarin	26	27	30	29	0.154	0.845
Digoxin	64	62	64	67	0.764	0.428
Spironolactone	9	12	13	16	0.233	0.205
Loop diuretics	84	87	83	80	0.336	0.107
Amiodarone	13	17	13	13	0.484	0.324
Vasodilator	13	12	13	7	0.143	0.152

Values are presented as percents or means (standard deviation) unless otherwise stated. ACE = angiotensin converting enzyme. ARB = angiotensin receptor blocker; BP = Blood Pressure; CCB = Calcium Channel Blockers; COPD = Chronic Obstructive Pulmonary Disease; DHP = Dihydropyridine; LBBB = left bundle branch block. LVH = left ventricular hypertrophy. NYHA = New York Heart Association. *Indicates p-value is for trend across quartiles of hemoglobin. **Indicates p-value is for comparison between patients above and below the median hemoglobin value of 131 g/L.

Table 4. Laboratory Values for 791 Heart Failure Patients.

	Quartile 1 Hemoglobin <119 g/L (n=197)	Quartile 2 Hemoglobin 119 to 131 g/L (n=202)	Quartile 3 Hemoglobin 132 to 144 g/L (n=202)	Quartile 4 Hemoglobin >144 g/L (n=194)	p*	p**
Hemoglobin (g/L)	107 (10)	125 (4)	138 (4)	152 (8)		
Potassium (mmol/L)	4.5 (0.5)	4.4 (0.5)	4.4 (0.5)	4.4 (0.5)	0.736	0.364
Sodium (mmol/L)	138 (4)	139 (3)	139 (3)	139 (4)	0.449	0.01
Creatinine (mmol/L)						
Mean (SD)	157 (110)	129 (60)	121 (54)	108 (28)	<0.001	<0.001
Median (IQR)	121 (97-171)	114 (92-149)	110 (89-131)	105 (90-120)		
CrCl (ml/min)	52 (33)	53 (30)	62 (32)	76 (39)	<0.001	<0.001
HbA1c§ (%)	7.1 (1.5)	7.4 (1.7)	7.6 (1.6)	8.0 (1.9)	0.187	0.055
TSH§ (mIU/L)	4.2 (10.3)	6.2 (12.1)	4.3 (8.1)	3.1 (2.8)	0.330	0.177
Iron indices§						
MCV (fL)	88 (7)	90 (6)	90 (5)	91 (5)	0.382	0.220
Ferritin (ug/L)	207 (424)	158 (169)	236 (354)	209 (159)	0.309	0.822
Saturation Index	0.20 (0.19)	0.22 (0.30)	0.13 (0.05)	0.30 (0.36)	0.762	0.820
TIBC (umol/L)	52 (14)	56 (18)	61 (13)	50 (12)	0.721	0.207
Serum iron (umol/L)	11 (12)	20 (26)	21 (34)	13 (15)	0.310	0.104

Values are means (standard deviation) unless otherwise stated. Creatinine Clearance is calculated from the Cockroft-Gault equation. CrCl = Creatinine Clearance; HbA1c = glycosylated hemoglobin; MCV = mean corpuscular volume; TIBC = total iron binding capacity; TSH = thyroid stimulating hormone. *Indicates p-value is for trend across quartiles of hemoglobin. **Indicates p-value is for comparison between patients above and below the median hemoglobin value of 131 g/L. §Indicates that values were not present on all patients (HbA1c available for 85 patients, TSH for 323 patients, MCV for 662 patients, ferritin for 118 patients, saturation index for 47 patients, TIBC for 47 patients and serum iron for 48 patients).

4.2 Definitions of Anemia

Hemoglobin had a normal distribution in this population, even when divided into gender (Figure 1). However, the median hemoglobin differed between males (135 g/L [IQR 119 to 144]) and females (125 g/L [IQR 115 to 136]) ($p<0.001$)(Table 5). After reviewing the hemoglobin normal distribution for the entire cohort, males and females separately, quartiles were created for all three groups.(Table 5) Of all patients with an available hemoglobin (n=791), 39% met the WHO definition for anemia and 45% met the CDC definition for anemia. Thirty-five percent of females met both the WHO and CDC definition for anemia, whereas 40% and 50% of males met the WHO or CDC definition, respectively. Of the 118 patients with all of hemoglobin, ferritin and MCV available, 47% met the definition of anemia of chronic disease; this was similar for females and males (47% and 46%, respectively). Of the 305 patients who met the WHO definition for anemia, 87% had a normocytic anemia (MCV 80 to 100 fl); this rate was similar between males (88%) and females (83%) and with other definitions used for anemia.

Figure 1. Hemoglobin distribution with line of normal distribution line also shown. Top panel: All patients (n=791); Middle panel: Male cohort (n=516); Bottom panel: Female cohort (n=275).

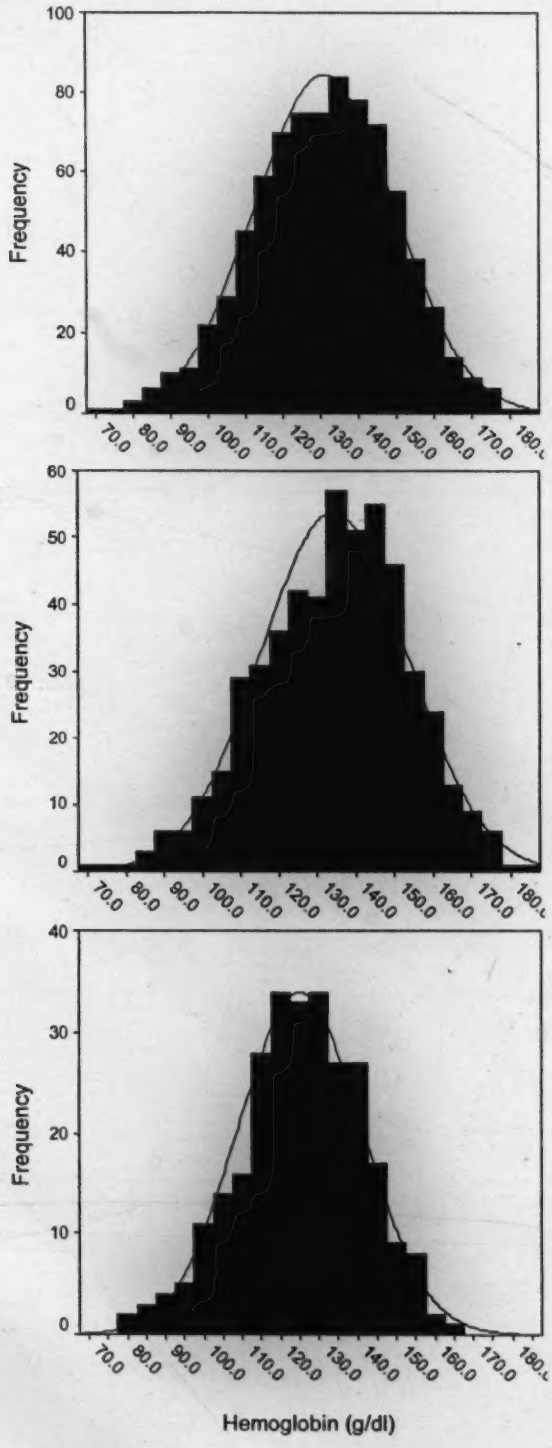


Table 5. Gender Relationship to Hemoglobin and Anemia Definitions.

	All patients (n=791)	Male (n=516)	Female (n=275)
Hemoglobin (g/L)			
Mean (SD)	131 (19)	134 (19)	125 (16)
25th percentile	119	121	115
50th percentile	131	135	125
75th percentile	144	148	136
Ferritin >18 µg/L	112/118 (95%)	69/69 (100%)	43/49 (88%)
Ferritin >45 µg/L	91/118 (77%)	58/69 (84%)	33/49 (67%)
MCV 80 to 100 fL	604/648 (93%)	389/423 (92%)	215/235 (92%)
WHO Definition	305/791 (39%)	208/516 (40%)	97/275 (35%)
CDC Definition	356/791 (45%)	259/516 (50%)	97/275 (35%)
Anemia of Chronic Disease	55/118 (47%)	32/69 (46%)	23/49 (47%)

Centers for Disease Control (CDC) definition is hemoglobin <120 g/L for females and hemoglobin <135 g/L for males. World Health Organization (WHO) definition is hemoglobin < 120g/L for females and hemoglobin <130 g/L for males. Anemia of Chronic Disease is defined by ferritin > 45 µg/L, MCV 80 to 100 fL, and meeting CDC criteria for anemia (<120 g/L for females. <135 g/L for males). MCV = mean corpuscular volume. All values given as n/N, (%) unless otherwise stated.

4.3 Survival

Survival at one, 2 and 5-years for the entire cohort was 73%, 57%, and 26% respectively. In the male cohort, 1, 2, and 5 year survival was 71%, 55% and 26% whereas it was 76%, 59% and 25% for females; this better survival in females trended towards significance for the entire period of follow-up (p=0.068). One-year and overall survival by quartile of hemoglobin for the entire cohort did demonstrate a graded risk, but was not statistically significant (p=0.11, p=0.09, Figure 2, Table 6). Using the WHO definition for anemia (<130 g/L for males, <120 g/L for females) for the entire cohort, the presence of anemia was associated with decreased survival for one-year (p=0.004), 2-years (p=0.0007) and over the entire follow-up period (p<0.0001, Figure 3).

Figure 2. Survival Curve for Entire Cohort by Quartile of Hemoglobin.

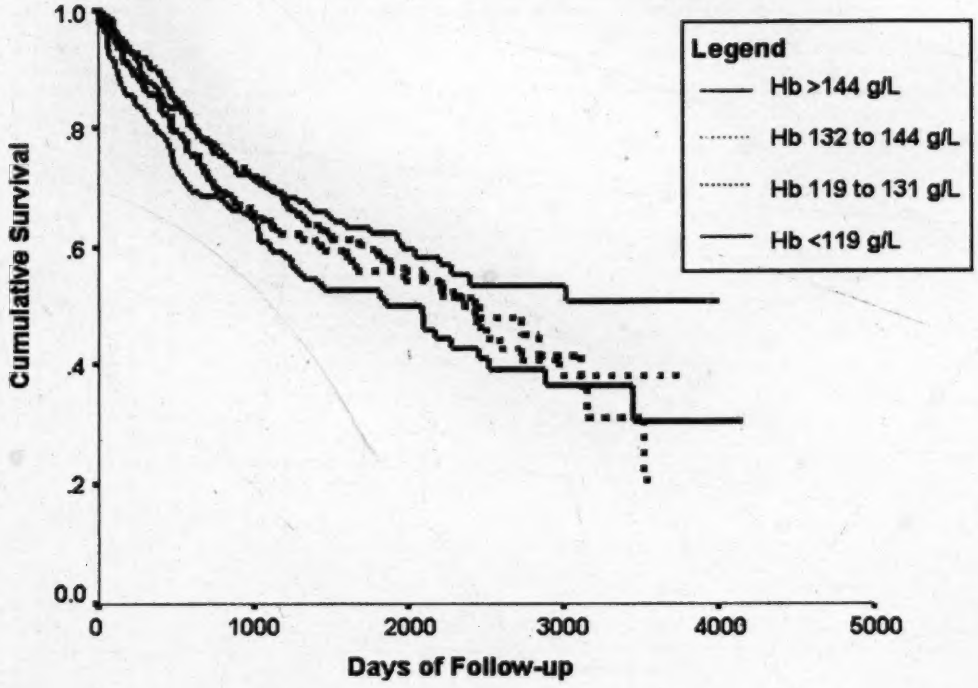


Figure 3. Survival Curve for Entire Cohort by WHO Definition for Anemia.

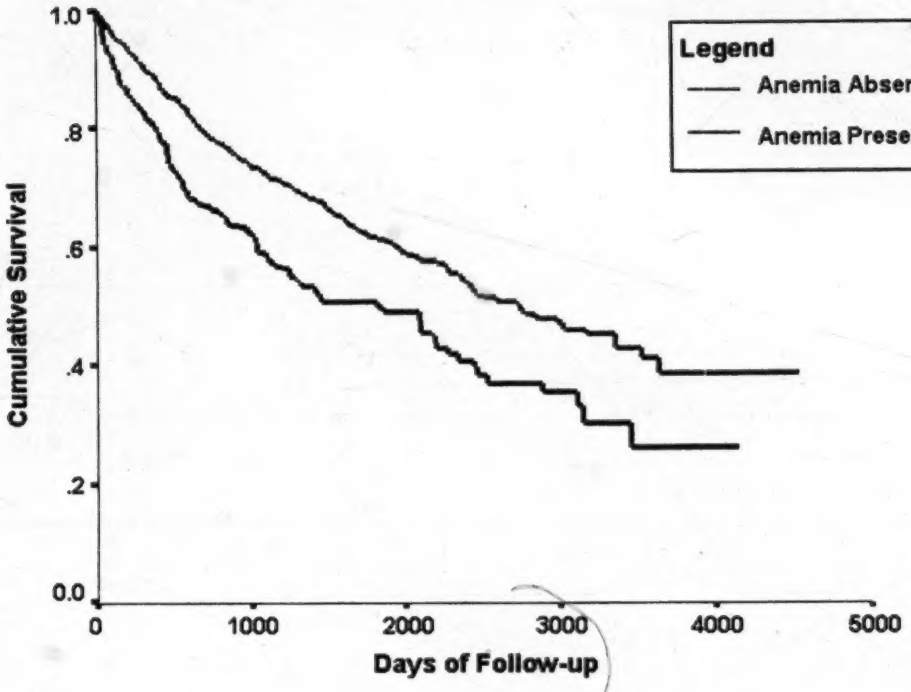


Table 6. The Association of Different Definitions for Anemia on 1-year, 2-year and 5-year Mortality.

	Male Patients (n=516)			Female Patients (n=275)		
	χ^2	p	Odds Ratio	χ^2	p	Odds Ratio
WHO Definition						
1-year	7.61	0.006	1.7 (1.12 to 2.50)	0.484	0.486	1.22 (0.69 to 2.16)
2-year	9.23	0.002	1.73 (1.21 to 2.46)	3.10	0.078	1.57 (0.95 to 2.59)
5-year	6.85	0.009	1.76 (1.15 to 2.7)	2.40	0.624	1.15 (0.65 to 2.05)
CDC Definition						
1-year	12.85	<0.001	2.0 (1.37 to 2.95)	0.484	0.486	1.22 (0.69 to 2.16)
2-year	13.18	<0.001	1.91 (1.35 to 2.71)	3.10	0.078	1.57 (0.95 to 2.59)
5-year	9.66	0.002	1.90 (1.26 to 2.86)	2.40	0.624	1.15 (0.65 to 2.05)
Quartiles of Hemoglobin**						
1-year	22.83	<0.001	Q1 1.91 (1.13 to 3.20) Q2 1.38 (0.82 to 2.34) Q3 0.82 (0.48 to 1.38)	0.840	0.840	Q1 1.02 (0.47 to 2.20) Q2 0.98 (0.45 to 2.11) Q3 0.73 (0.33 to 1.64)
2-year	15.48	0.001	Q1 1.64 (1.01 to 2.68) Q2 1.52 (0.93 to 2.48) Q3 0.67 (0.41 to 1.12)	1.621	0.655	Q1 1.26 (0.63 to 2.49) Q2 1.13 (0.57 to 2.23) Q3 0.82 (0.41 to 1.65)
5-year	7.205	0.066	Q1 2.07 (1.15 to 3.71) Q2 1.76 (1.00 to 3.11) Q3 1.00 (0.59 to 1.70)	0.959	0.811	Q1 1.25 (0.56 to 2.77) Q2 1.02 (0.47 to 2.20) Q3 0.85 (0.40 to 1.81)
Anemia of Chronic Disease	0.781	0.377	1.39 (0.67 to 2.88)	1.455	0.228	1.70 (0.71 to 4.06)
Hemoglobin <110 g/L	2.252	0.133	1.53 (0.88 to 2.66)	5.786	0.016	2.15 (1.14 to 4.0)
Hemoglobin <115 g/L	0.634	0.426	1.21 (0.76 to 1.90)	1.927	0.165	1.49 (0.85 to 2.63)
Hemoglobin <120 g/L	1.878	0.171	1.33 (0.88 to 1.99)	1.545	0.214	1.39 (0.83 to 2.35)
Hemoglobin <125 g/L	4.692	0.030	1.51 (1.04 to 2.20)	0.906	0.341	1.28 (0.77 to 2.12)
Hemoglobin <130 g/L	5.089	0.024	1.51 (1.06 to 2.16)	0.008	0.928	0.98 (0.58 to 1.64)

Anemia of Chronic Disease is a comparison for 1-year mortality. Hemoglobin cut-offs for hemoglobin <110 g/L, <115 g/L, <120 g/L, <125 g/L, <130 g/L are for comparisons below/above this value for 1-year mortality. WHO = World Health Organization; CDC = Centers for Disease Control; Hb=hemoglobin; Q2 = quartile 2 (119 to 131 g/L); Q3 = quartile 3 (132 to 144 g/L); Q4 = quartile 4 (>144 g/L). *Indicates p-value is for trend. **Reference is highest quartile of hemoglobin (Q4).

After separating the cohort into a male-only and a female-only cohort (and using their respective hemoglobin quartiles), different definitions for anemia were dissociated with survival and genders.(Figures 4 to 9, Table 6) In males, the WHO definition was associated with mortality at 1-year (OR 1.7 [1.12 to 2.50]), 2-years (OR 1.73 [1.21 to 2.46]) and 5-years (OR 1.76 [1.15 to 2.7]); the results for the CDC definition were similar with an almost two-fold risk of mortality if hemoglobin was less than 135 g/L.(Table 6, Figures 4 to 6) Analysis of the hemoglobin quartiles for male patients with 1-year, 2-year, 5-year and overall mortality revealed a similar trend for higher mortality across the quartiles (p <0.001, 0.001, 0.066, 0.001 respectively).(Table 6, Figure 4) No differences

in survival were seen whether or not anemia of chronic disease was present (versus those who had anemia of another cause) for males.

Figure 4. Survival Curve for Male Cohort by Quartile of Hemoglobin.

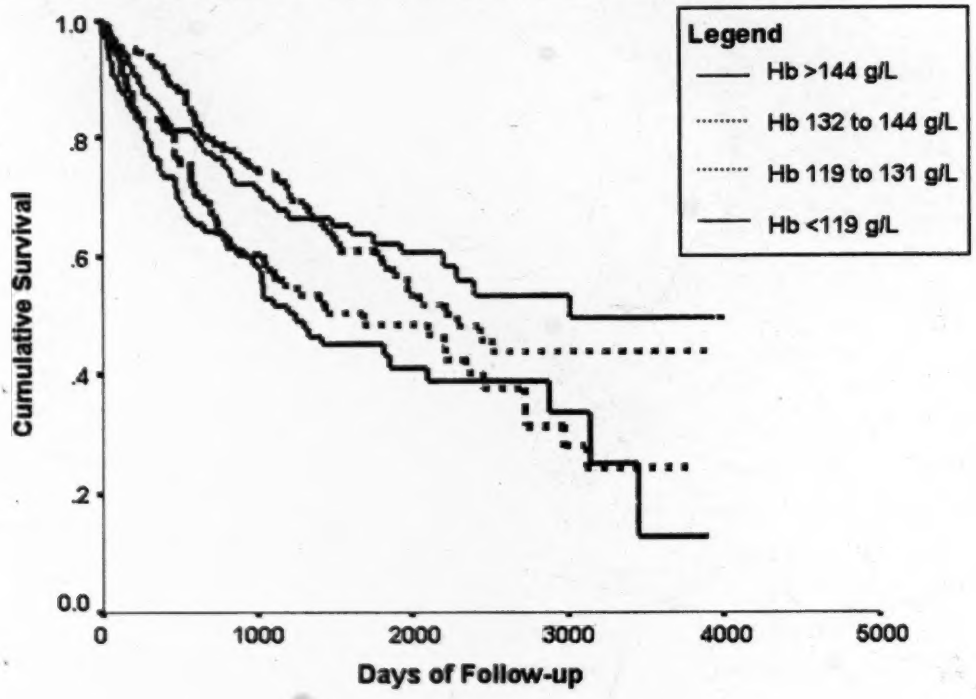


Figure 5. Survival Curve for Male Cohort by CDC Definition for Anemia.

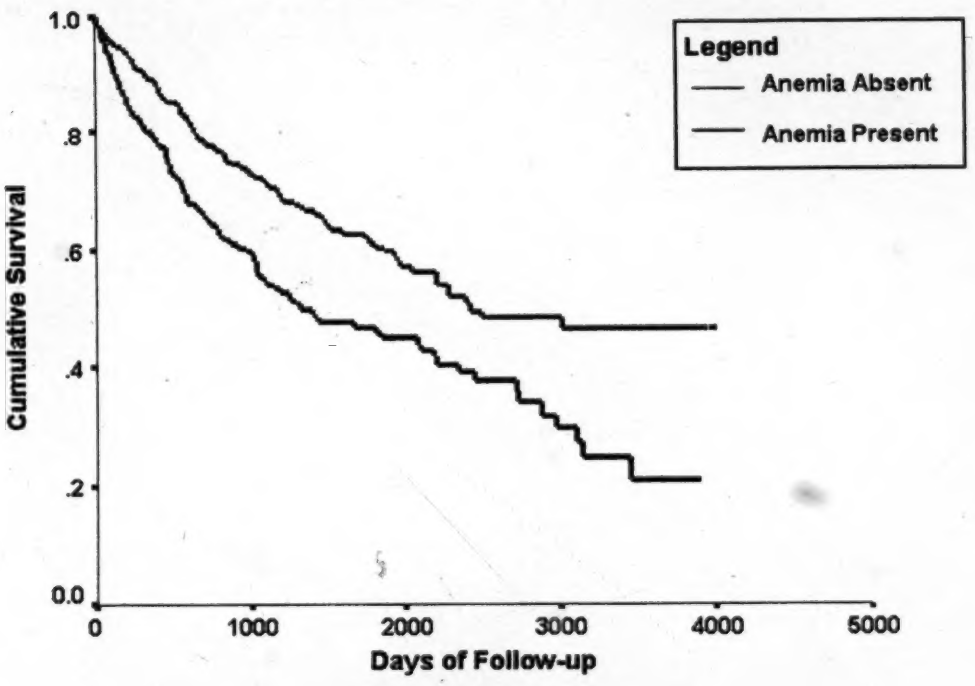
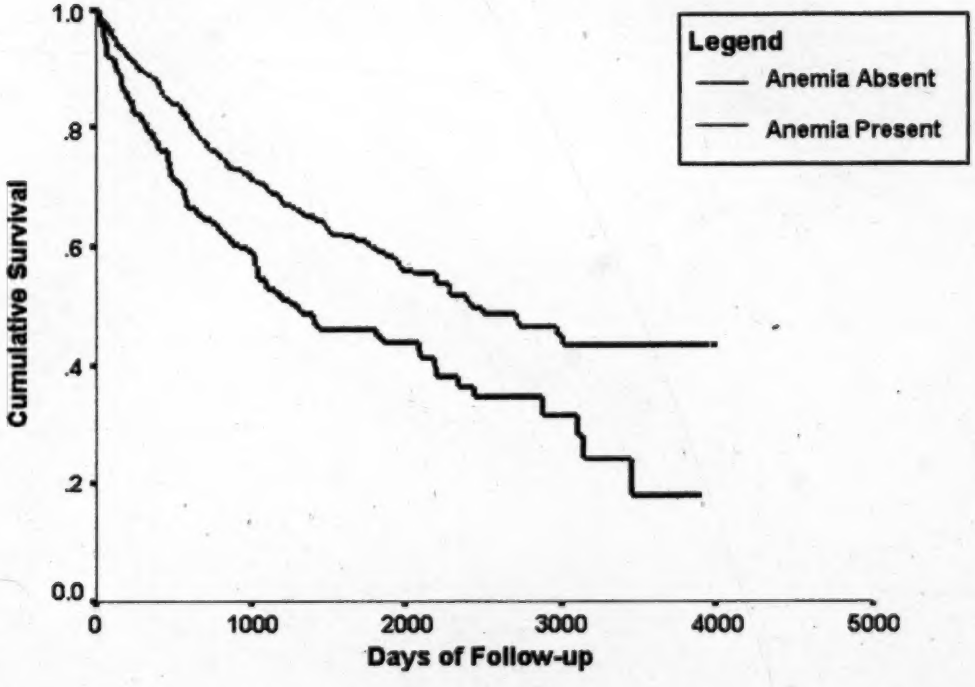


Figure 6. Survival Curve for Male Cohort by WHO Definition for Anemia.



In females, the association of quartiles of hemoglobin and mortality for females was non-significant.(Figure 7); furthermore, the WHO or CDC definitions were not associated with increased mortality at 1-year, 2-years, 5-years or during the entire follow-up period. (Figure 8) Only the 2-year survival trended toward significance (p=0.078, OR 1.57 [0.95 to 2.59]). No differences in survival were seen whether or not anemia of chronic disease was present or absent for females. Finally, no difference in survival was seen when the median hemoglobin for females (125 g/L) was used (p=0.28).(Figure 9)

Figure 7. Survival Curve for Female Cohort by Quartile of Hemoglobin.

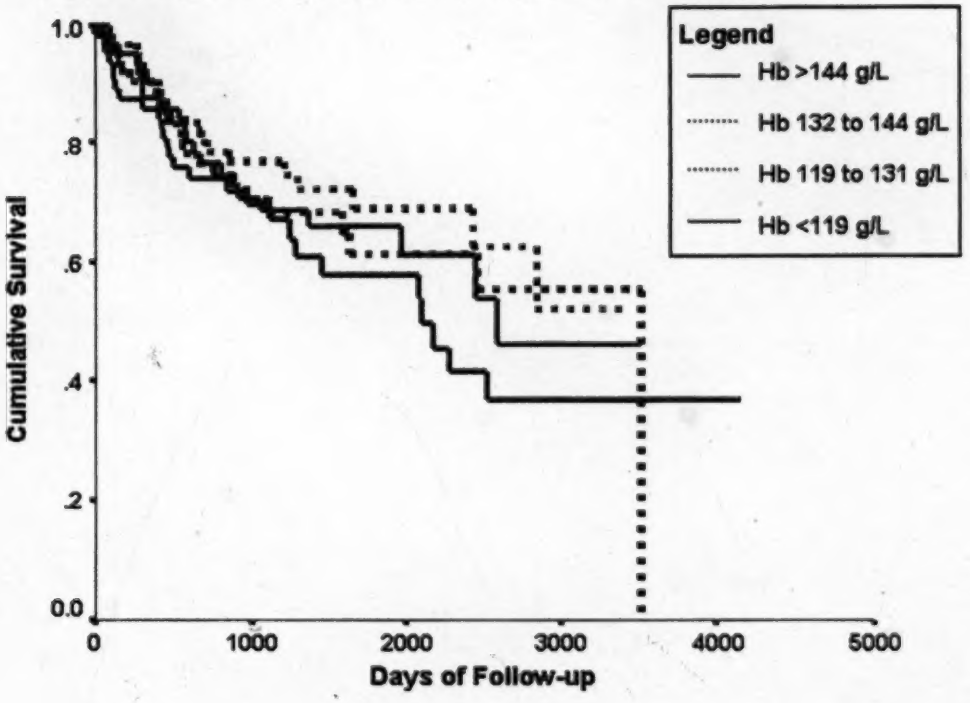


Figure 8. Survival Curve for Female Cohort by CDC/WHO Definition for Anemia.

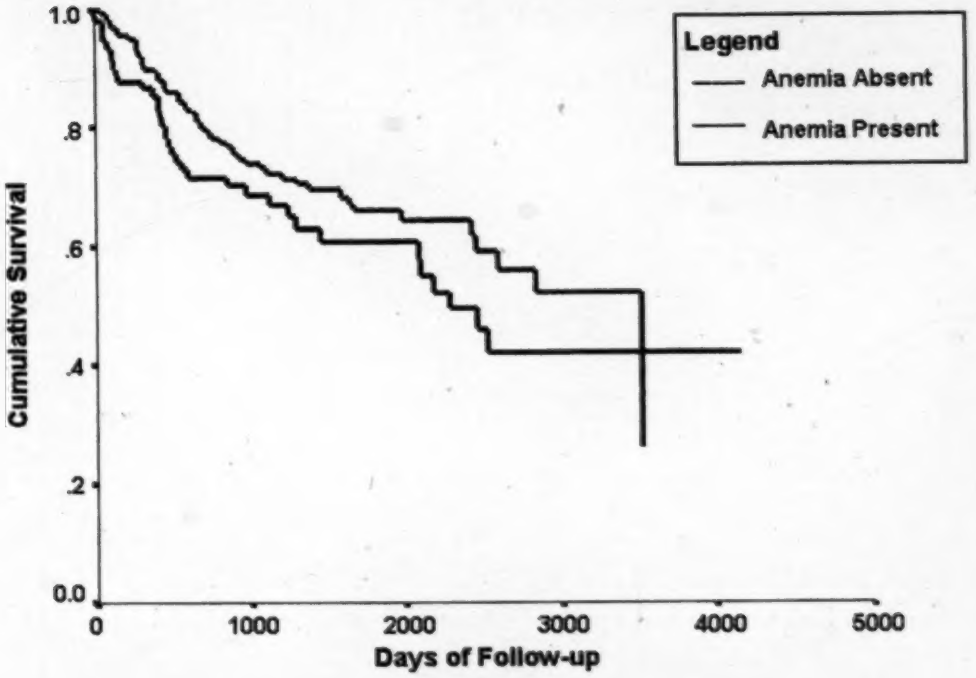
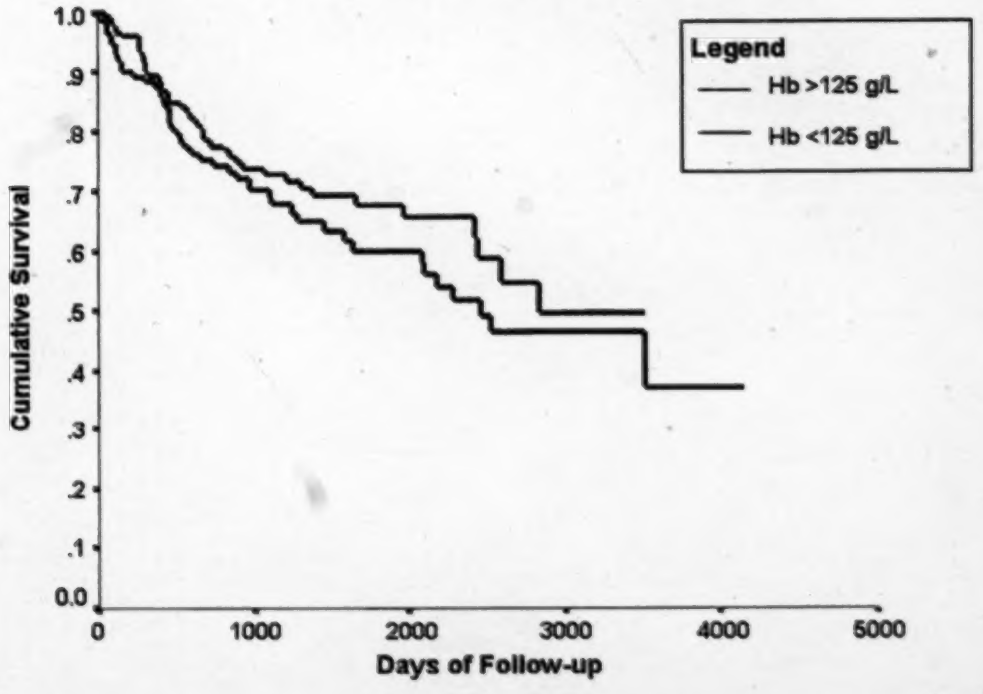


Figure 9. Survival Curve for Female Cohort by Median Hemoglobin.



4.5 Multivariate Regression for 1-Year and Overall Mortality

4.5.1 All Heart Failure Patients

The adjusted multivariate analyses are shown in Table 7 and Table 8, for 1-year and overall mortality, respectively. Univariate predictors of 1-year and overall mortality for all 1037 heart failure clinic patients are shown in Appendix E.

For 1-year mortality, after adjustment for covariates and baseline characteristics using a multivariate logistic regression model, a higher hemoglobin was protective (OR 0.99 per g/L Hb increase [95%CI 0.98 to 1.00], as was female gender (OR 0.50 [95%CI 0.32 to 0.78]), treatment with beta-blockers (OR 0.42 [95%CI 0.27 to 0.65]), aspirin (OR 0.49 [95%CI 0.33 to 0.76]) or vasodilators (OR 0.17 [95%CI 0.05 to 0.55]).(Table 6) NYHA Class III/IV at first visit predicted 1-year mortality (OR 2.00 [95%CI 1.32 to 3.04]), and Creatinine Clearance (with severe renal impairment [<30 ml/min] as the reference) predicted 1-year survival, with increasing creatinine clearance improving the odds of 1-year survival (normal CrCl OR 0.37 [95%CI 0.18 to 0.78]).

Table 7. Multivariate Predictors of 1-year Mortality using Logistic Regression.

Variable	p	Odds Ratio	95%CI
Female	0.002	0.50	0.32 to 0.78
NYHA Class III/IV	0.001	2.00	1.32 to 3.04
Beta-Blockers	<0.001	0.42	0.27 to 0.65
Aspirin	0.001	0.49	0.33 to 0.76
Vasodilator	0.003	0.17	0.05 to 0.55
Creatinine Clearance			
Severe (<30 ml/min)	Reference		
Moderate (30 to 59 ml/min)	0.124	0.66	0.39 to 1.12
Mild (60 to 90 ml/min)	0.001	0.35	0.18 to 0.67
Normal (>90 ml/min)	0.009	0.37	0.18 to 0.78
Hemoglobin (per g/L increase)	0.023	0.99	0.98 to 1.00

Creatinine Clearance reference value is Severe Renal Insufficiency (<30 ml/min). Reference category is NYHA Class I/II for NYHA Class III/IV. NYHA = New York Heart Association; ACE = angiotensin converting enzyme; 95%CI = 95% Confidence Interval.

For overall mortality, after adjustment for important covariates and baseline characteristics using a proportional hazards model, a higher or lower hemoglobin was neither protective or harmful (HR 0.99 per g/L Hb increase [95%CI 0.99 to 1.00].(Table 8) Female gender predicted overall survival (HR 0.49 [95%CI 0.37 to 0.64]), as did treatment with beta-blockers (HR 0.58 [95%CI 0.45 to 0.76]), angiotensin-converting

enzyme inhibitors (HR 0.72 [95%CI 0.51 to 1.01]), spironolactone (HR 0.06 [95%CI 0.01 to 0.45]) and vasodilators (HR 0.44 [95%CI 0.25 to 0.79]). Higher creatinine clearance also predicted overall survival (HR 0.99 per ml/min increase in CrCl [95%CI 0.98 to 1.00]). NYHA Class III/IV at first visit predicted overall mortality (HR 1.75 [95%CI 1.35 to 2.27]), as did systolic dysfunction (HR 1.46 [95%CI 1.08 to 1.98]) and older age (HR 1.02 per year increase [95%CI 1.00 to 1.03]).

Table 8. Multivariate Predictors of Overall Mortality, using a Proportional Hazards Model.

Variable	p	Hazard Ratio	95%CI
Age (per year increase)	0.006	1.02	1.00 to 1.03
Female	<0.001	0.49	0.37 to 0.64
NYHA Class III/IV	<0.001	1.75	1.35 to 2.27
Systolic dysfunction	0.015	1.46	1.08 to 1.98
Beta-Blockers	<0.001	0.58	0.45 to 0.76
ACE inhibitor	0.058	0.72	0.51 to 1.01
Spironolactone	0.006	0.06	0.01 to 0.45
Vasodilator	0.006	0.44	0.25 to 0.79
Creatinine Clearance (per ml/min increase)	0.01	0.99	0.98 to 1.00
Hemoglobin (per g/L increase)	0.156	0.99	0.99 to 1.00

Reference category is NYHA Class I/II for NYHA Class III/IV. NYHA = New York Heart Association; ACE = angiotensin converting enzyme; 95%CI = 95% Confidence Interval.

4.5.2 Male Heart Failure Patients

For overall mortality, using a proportional hazards model in male patients of this cohort, left bundle branch block (HR 1.85 [95%CI 1.11 to 3.08]) and NYHA Class III/IV (HR 1.71 [1.06 to 2.77] were associated with increased mortality whereas spironolactone (HR 0.05 [95%CI 0.01 to 0.08]) and increased creatinine clearance (HR 0.98 per ml/min increase in CrCl [95%CI 0.98 to 0.99]) were associated with reduced mortality. When anemia definitions were added into this model (forced in or added last), neither the CDC nor the WHO definition were significant predictors of overall mortality in this model (HR 1.2 [95%CI 0.74 to 1.94]; HR 1.15 [95%CI 0.7 to 1.89], respectively). When different hemoglobin cut-offs were used to further explore the relationship between hemoglobin and overall mortality in this model, none of cut-offs of 110 g/L (HR 1.24 [95%CI 0.54 to 2.87]), 120 g/L (HR 1.1 [95%CI 0.54 to 1.64]), 125 g/L (HR 1.4 [95%CI 0.82 to 2.37]), or 140 g/L (HR 1.45 [95%CI 0.9 to 2.34]) added to the model to predict overall mortality.

A separate model was created for 1-year mortality (for males only), in which the presence of atrial arrhythmias (OR 1.88 [95%CI 1.01 to 3.52], ventricular arrhythmias (OR 1.884 [95%CI 1.00 to 3.53]) and NYHA Class III/IV (OR 2.71 [1.49 to 4.92] were associated with increased mortality whereas spironolactone (OR 0.05 [95%CI 0.01 to 0.08]), digoxin (OR 0.54 [95%CI 0.28 to 1.02]), and beta-blockers (OR 0.34 [95%CI 0.18 to 0.67] were protective. When various hemoglobin definitions were used (forced in or added last to this model), none of 110 g/L (OR 0.67 [95%CI 0.23 to 1.98]), 115 g/L, 120 g/L (OR 1.63 [95%CI 0.85 to 3.15]), 125 g/L (OR 1.34 [95%CI 0.72 to 2.49], 130 g/L (OR 1.04 [95%CI 0.57 to 1.90]), 135 g/L (OR 1.25 [95%CI 0.7 to 2.24]), or 140 g/L (OR 0.98 [95%CI 0.54 to 1.77]) added to the model to predict 1-year mortality. In addition, the interaction terms edema*hemoglobin and edema*anemia did not add significantly to the predictive multivariate model, and addition of edema to the overall model did not change the beta coefficients indicating the absence of confounding by edema.

4.5.2 Female Heart Failure Patients

For overall mortality, using a proportional hazards model in female patients of this cohort, left bundle branch block (HR 2.22 [95%CI 1.19 to 4.13]) was associated with a higher mortality; treatment with beta-blockers (HR 0.36 [95%CI 0.19 to 0.67] and spironolactone (HR 0.20 [95%CI 0.02 to 1.67] were associated with lower mortality as was increased creatinine clearance (HR 0.98 per ml/min increase in CrCl [95%CI 0.97 to 1.00]. When various hemoglobin definitions were used (forced in or added last to this model), only hemoglobin as a continuous variable was associated with a lower overall mortality (HR 0.99 per one g/L increase in hemoglobin [95%CI 0.97 to 1.00]. However, none of definitions of anemia using cut-offs of 100 g/L (HR 0.69 [95%CI 0.17 to 2.85], 110 g/L (HR 3.56 [95%CI 0.84 to 15.17]), 115 g/L (HR 0.64 [95%CI 0.15 to 2.79]), 120 g/L (HR 0.83 [95%CI 0.26 to 2.67]), 125 g/L (HR 2.79 [95%CI 0.78 to 10.03], 130 g/L (HR 0.35 [95%CI 0.17 to 2.85]), 135 g/L (HR 1.15 [95%CI 0.71 to 2.34]), or 140 g/L (HR 1.27 [95%CI 0.59 to 2.74]) added to the model to predict overall mortality.

A separate model was created for 1-year mortality (for females only), in which a history of ischemia (OR 2.08 [95%CI 0.90 to 4.77]) and sodium less than 135 mmol/L (OR 3.21 [95%CI 1.00 to 10.33] were associated with an increased mortality and

treatment with beta-blockers (OR 0.35 [95%CI 0.16 to 0.77] reduced mortality. When various hemoglobin definitions were used (forced in or added last to this model), none of definitions of anemia or hemoglobin as a continuous variable (OR 1.01 per one g/L increase in hemoglobin [95%CI 0.98 to 1.04], 100 g/L (OR 0.43 [95%CI 0.8 to 2.37], 110 g/L (OR 0.85 [95%CI 0.33 to 2.18]), 115 g/L (OR 0.85 [95%CI 0.37 to 1.97]), 120 g/L (OR 1.31 [95%CI 0.62 to 2.75]), 125 g/L (OR 1.31 [95%CI 0.63 to 2.74], 130 g/L (OR 0.99 [95%CI 0.46 to 2.15]), 135 g/L (OR 1.15 [95%CI 0.71 to 2.34]), or 140 g/L (OR 1.17 [95%CI 0.47 to 2.95]) added to the model to predict 1-year mortality.

4.6 Testing for Interaction

Interactions between gender, mortality, and various definitions for anemia were tested using the Mantel-Haenszel test for homogeneity. For hemoglobin above or below the median (131 g/L) for the outcome of 1-year mortality, stratified by gender, the Mantel-Haenszel test was significant (χ^2 4.39, p=0.03). Similarly, for the WHO definition was used, the Mantel-Haenszel test was significant (χ^2 7.50, p=0.006), as was the CDC definition (χ^2 6.88, p=0.009). For the outcome of 2-year mortality, the WHO definition was heterogeneous (χ^2 8.06, p=0.005) as was the CDC definition (χ^2 8.99, p=0.003); all other time points were similar. These results indicate that the odds ratios should not be pooled, as they will have no meaning since the data is heterogeneous between genders for anemia.

Chapter 5: Discussion

5.1 Gender Differences

In patients with congestive heart failure optimally managed with evidence-based medications, anemia is an important prognostic risk factor – however this risk is dependent on gender. In our cohort, 35% of females met the WHO/CDC definition for anemia but one, two or five-year survival for patients with anemia was not impaired. Moreover only after taking into account the entire follow-up period was a higher hemoglobin associated with a lower mortality (HR 0.99 per one g/L increase in hemoglobin [95%CI 0.97 to 1.00]) in females. This is in contrast to the male cohort, in which survival was impaired by the presence of anemia, imparting an almost twofold risk for 1-year, 2-year and 5-year mortality using the CDC definition and an odds ratio of 1.7, 1.73 and 1.76 for the WHO definition over the same time period. Since our cohort was 2/3 male, this imbalance resulted in statistical heterogeneity and the results for mortality using Chi-square technique would be invalid, resulting in the potentially erroneous conclusions of the non-significance of anemia as a risk factor in congestive heart failure. It should be noted that this interaction was not present for the multivariate regression, where the interaction term of gender and anemia was not significant in the final model.

Only Kosiborod has evaluated the differences in anemia prevalence by gender, with approximately 20% of females having a hematocrit <32%, and 50% having a hematocrit<37%.[42] Although the prevalence of anemia in our cohort was similar to the findings of Kosiborod et al., our study failed to demonstrate that the level of hemoglobin had a significant impact on survival in females with heart failure. Importantly, Kosiborod did not examine the difference in survival by gender, and utilized the same non-standard anemia definition for both genders. In an Alberta database analysis of new-onset heart failure patients, this interaction was not noted; this difference may be due to the relative differences between populations studied. These differences are likely threefold: (1) the Alberta population was hospitalized which incurs a higher mortality risk regardless of gender; (2) medication use was not known; (3) and the mean age of patients was 77 years in the Alberta database versus 68 years in this analysis. When the individual cohorts from our clinic are examined, anemia is clearly an important risk

factor for male heart failure patients; the lack of an apparent impact of anemia in female patients with congestive heart failure requires further exploration.

At least part of the reason for this discordance is that female heart failure patients have previously be shown to have a better survival than male patients in both the Framingham cohort[79] and recent clinical trials.[80] In our clinic, the 1-year survival was 76% for females and 71% for males; this difference persisted over the entire follow-up period and despite equal distribution of evidence-based medications and a four-year difference in the mean age (female mean age 69 years [SD 14], male mean age 65 years [SD 14], $p<0.001$). This better survival in the female cohort may have provided too few deaths to demonstrate that hemoglobin and/or anemia plays a role as a risk factor for mortality.

5.2 Ejection Fraction

Patients from our clinic with a hemoglobin value below 131 g/L (versus those above 131 g/L) had a higher ejection fraction, suggesting that patients with diastolic heart failure may be at equal or higher risk for developing anemia than those with systolic heart failure. Although ejection fraction was not predictive of mortality in the multivariate model, systolic dysfunction (versus diastolic dysfunction) was predictive of overall mortality with a hazard ratio of 1.5, indicating that patients with systolic dysfunction have a worse outcome. In the only other study that has included patients (1/3 of their cohort) with a higher ejection fraction, an EF of <20% (versus the reference of >40%) was associated with 1-year mortality with a hazard ratio of 1.52 (95%CI 1.20 to 1.86).[42] That study, however, was hampered by the 24% who had no evaluation of ejection fraction, who also had a hazard ratio of 1.50 (95%CI 1.27 to 1.83), suggesting that these patients represented a cohort at increased risk in whom diastolic or systolic heart failure may have been present. Recent evidence has reported the poor outcomes of individuals with diastolic heart failure with annual mortality rates approaching those of systolic heart failure, highlighting the need for accurate diagnosis of correctable or treatable co-morbidities in both forms of heart failure.[7,70] Importantly, in our study, NYHA Class III or IV was a significant predictor of 1-year and overall mortality after adjustment for important baseline characteristics, suggesting that symptoms, but not ejection fraction, are sensitive markers for patients at risk for death with both anemia and heart failure.

Putative mechanisms as to the cause of anemia in systolic versus diastolic heart failure are likely similar, but definitive research has not been done.

5.3 Etiology of Heart Failure

Anemic patients were more likely to have an ischemic etiology for their heart failure; this is consistent with previous work.[41,42,50] The role of inflammatory markers, therapeutic strategies, and other concomitant conditions may differ in ischemic heart failure; alternatively, hibernating myocardium in patients with underlying ischemic etiology for their heart failure may play a role in cellular signalling to the bone marrow by an unknown mechanism. There is accumulating evidence that the hormone that stimulates development and maturation of erythroid cells (erythropoetin) has a role in the myocardium. Erythropoetin is known to stimulate myoblast proliferation and differentiation in mouse models, and the erythropoetin receptor is a member of the cytokine receptor superfamily.[81] Erythropoetin acts through an important pathway for heart failure, Jak2 and Stat5, suggesting a common pathway maybe involved in the regulation of downstream processes that could involve both known heart failure elements and novel elements, such as erythropoetin.[82] Furthermore, erythropoetin is expressed in the embryonic heart, with Epo-knockout mice suffer from ventricular hypoplasia and a reduction in proliferating cardiac myocytes, both independent of hypoxia.[81,83] These mechanisms by which myocardial cells signal each other and start apoptotic processes can be different, based on the primary etiology of the heart failure;[84] the signalling pathways in ischemic myocardium may be differentially effected by the alteration of the erythropoetin pathway. The pathways for signalling between cells and organs are intimately related in congestive heart failure, and it is likely that these pathways are linked in congestive heart failure and anemia.

5.4 Renal Function

Anemia has a consistent relationship to renal function as a predictor of mortality across clinical trials[43], community databases[43,45,50]and other specialty clinic analyses[41,47], and our results are consistent with this. The relationship of renal function to mortality has been consistent in these analyses, and the worsening renal function portends a poor outcome in congestive heart failure.[12] Furthermore, creatinine clearance as calculated by

the Cockroft-Gault strongly predicts patients at risk for developing anemia as well as having an increased risk for poor outcomes. Anemia in renal failure is proportional to the severity of renal failure, although there is no strict linear relationship between hematocrit and creatinine clearance. The kidney has a direct role in red blood cell production by the production of erythropoetin in the juxtaglomerular apparatus in the afferent arteriole. Other mechanisms for anemia in renal failure include reduced red cell survival, blood loss and marrow suppression, related to toxic metabolic end products. Diminished renal perfusion also leads to activation of the renin-angiotensin axis increasing angiotensin II (resulting in myocardial remodelling and other downstream effects) and aldosterone (inducing myocardial fibrosis), both of which are associated with increased mortality in heart failure patients. Whether or not the anemia precedes renal dysfunction or anemia is in part the result of renal dysfunction is not known; careful longitudinal studies of heart failure patients will help elucidate the answer.

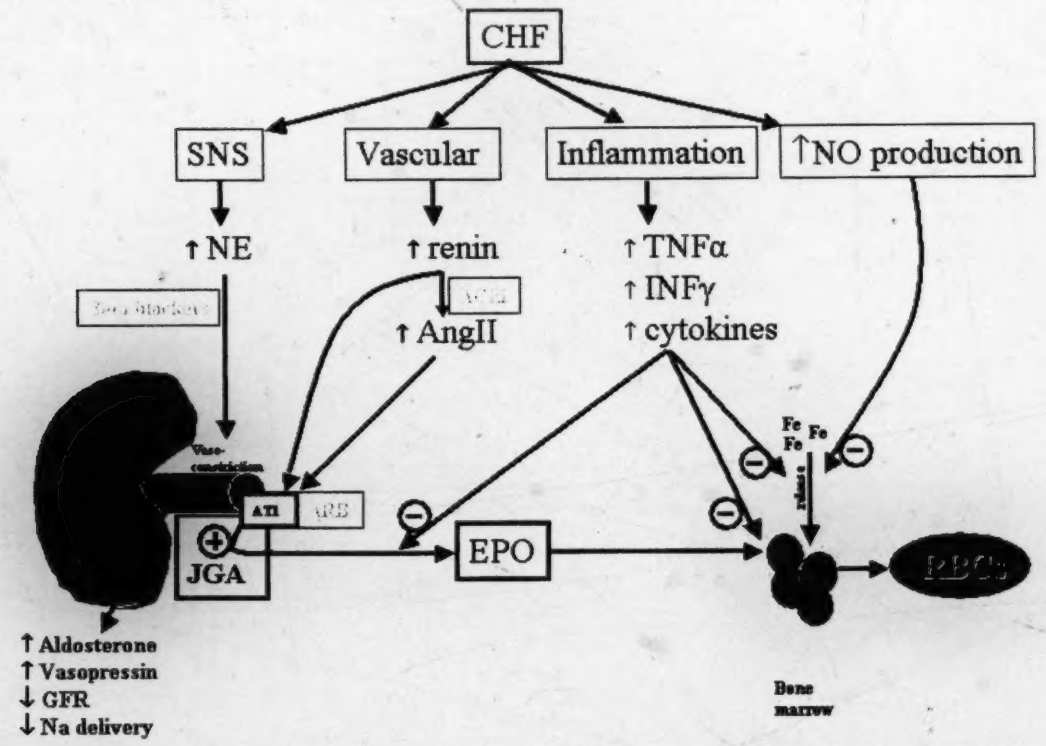
5.5 Anemia of Chronic Disease

A second and novel principal finding of this study is that anemia of chronic disease, when looked for in a carefully defined population with strict biochemical definitions, is prevalent. This is consistent with a recent analysis of community-based heart failure patients (n=12,065), conducted by my colleagues and I, using an administrative database – in this population, 58% had anemia of chronic disease and the same poor outcome as those with other causes of anemia, even after adjustment for important covariates (HR 1.34 [95%CI 1.23 to 1.50]).[50] Our overall prevalence of anemia of chronic disease of 47% is in keeping with the above estimate, albeit in a smaller but better-defined population using a prospectively defined biochemical definition. The causes for anemia of chronic disease in congestive heart failure are likely to be similar to other diseases where TNF- α plays a prominent role including rheumatoid arthritis.[85]

5.6 Pathophysiology of Anemia in Heart Failure

The basic pathophysiologic mechanisms that cause anemia in CHF are unknown and complex, likely modulated in part by many inflammatory mediators.(Figure 10)

Figure 10. Pathophysiology of Anemia in Congestive Heart Failure.



Legend. ACEi = angiotensin-converting enzyme inhibitor; AngII = angiotensin II; ARB = angiotensin receptor blocker; AT1 = angiotensin 1 receptor; CHF = congestive heart failure; EPO = erythropoietin; Fe=iron; GFR = glomerular filtration rate; INF = interferon gamma; JGA = juxtaglomerular apparatus; NE = norepinephrine; NO = nitric oxide; RBCs = red blood cells; TNF = tumor necrosis factor.

A variety of mechanisms have been proposed, including an inflammatory state characterized by cytokines, TGF-β, TNF-α and Interferon-γ. TNF- α is known to be elevated in CHF[62] and has been implicated in anemia of chronic disease.[63-65] Interferon-γ directly inhibits erythroid progenitor cells capacity for erythropoesis; this may be mediated in part by nitric oxide which blocks heme biosynthesis.[61,66] In addition, there are likely modulating roles for erythropoietin resistance[61], the renin-angiotensin axis[59]and medications such angiotensin-converting enzyme inhibitors[60]. Recently, Gossman et al. demonstrated that angiotensin II infusions to healthy male volunteers produced detectable increases in erythropoietin, which could be blocked via the use of an angiotensin-

receptor- blocker, valsartan. Finally, a randomized trial of angiotensin-converting-enzyme inhibitors in altitude polycythemia, where red cell production and erythropoietin increases are the result of chronic hypoxia, demonstrated that not only did hemoglobin and packed cell volume decrease, but proteinuria also decreased, independent of blood pressure lowering effects.[86] We were unable to demonstrate that anemia was associated with the use of either angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers. In fact, the lowest quartile of hemoglobin was associated with the lowest use of angiotensin-converting-enzyme inhibitors. It is not clear if this is due to selection bias or other biases in prescribing or if truly, no difference exists.

Two other classes of medications deserve consideration: anti-platelet and anti-thrombotic agents. Aspirin and warfarin have been linked to microscopic gastrointestinal blood loss as well as minor and major gastrointestinal hemorrhage leading to iron-deficiency anemia. We saw no differences in this cohort, and indeed, the rates of use of both these medications was 70% for aspirin and 47% for warfarin, and 27% of patients were on both medications. The use of these medications was similar across the quartiles of hemoglobin and when combined use of aspirin and warfarin was included in the multivariate model, it was not a significant predictor for mortality. In the only analysis to evaluate the incidence of iron-deficiency anemia, 16% of those who were anemic and heart failure had iron-deficiency anemia.[50]

5.7 Therapeutic Considerations

Regardless of the underlying mechanistic cause[s] for anemia associated with congestive heart failure, treatment of the underlying heart failure with appropriate evidence-based therapies should be the primary goal until appropriate testing of novel therapies have been completed. Ultimately elucidation of the putative cellular mechanisms for the associated anemia may lead to more specific corrective clinical strategies, but initial strategies of using erythropoietin have been attempted with success. In an open-label observational study of 32 patients from a specialty clinic, treatment of patients with both anemia and CHF with recombinant subcutaneous erythropoetin (EPO) and intravenous (IV) iron improved functional status.[47] In a randomized single-blind, placebo-controlled trial in 26 patients followed for 6 months, maximal exercise capacity, exercise duration, and quality of life improved with subcutaneous erythropoetin.[87] These

initial studies demonstrate the feasibility and potential impact on physiological outcomes and symptoms in anemic heart failure patients. Adequately powered randomized clinical trials need to be completed, using clinically meaningful endpoints and are in progress.

5.8 Limitations

Several limitations of this study require attention. Due to the retrospective nature of this study, we were unable to collect hemoglobin or other biochemical data on all patients and we excluded patients without a hemoglobin value from our analyses. However, the 76% of patients with an acceptable hemoglobin value were similar in age, gender, ischemic history, NYHA Class, systolic dysfunction, ejection fraction and mortality rate to those that did not have a hemoglobin value in the database. As well, the data for this clinic was prospectively designed, implemented and collected according to pre-specified criteria with strict clinical definitions of etiology of heart failure and other important clinical variables. Furthermore, the definitions for both congestive heart failure and anemia were prospectively determined. The definitions in this research are also well validated in the literature for both healthy and diseased populations and include two widely accepted definitions for anemia from respected international medical organizations (World Health Organization, Centers for Disease Control). Due to the nature of a specialty clinic for treating patients with congestive heart failure, there is inherent referral bias: few patients without symptoms are referred to this clinic, and fewer females are referred for care when compared to males. However, nearly 80% of patients were NYHA symptom Class II or III, and 35% of patients were female – the highest percentage reported from a specialty clinic in this research area. This clinic is different from those in a clinical trial as the clinic sees older patients, with extensive comorbities (including renal dysfunction) that would likely exclude them from a trial and more importantly, also sees patients with heart failure with preserved systolic function – both of these features lend a broader generalizability to our analysis.

We also note that our model included creatinine clearance as calculated by the Cockroft-Gault formula, which includes age, weight, and gender as weighted variables in the formula. Concern could be raised that the variables appearing in the formula should not be included as individual variables for the overall multivariate regression models.

While this is a concern, the addition of these three variables was still significant in the model, and the variables in the equation are only partially represented.

We were able to exclude a cause-effect relationship of anemia "causing" heart failure by accurate diagnostic and etiological classification of heart failure by standardized methods – as well, heart rate, TSH, and blood pressure were not significantly different between those who were anemic and those who were not. Finally, our definition of anemia of chronic disease is not supported directly with bone marrow morphology and iron stains. However, we used accepted biochemical definitions to define anemia of chronic disease using both the ferritin and mean corpuscular volume.[76,77]

Chapter 6: Conclusions

Anemia is prevalent in patients with heart failure, with 1/3 to ½ of patients with heart failure having this co-morbidity, ½ of which will have anemia of chronic disease. Anemia is an important risk factor for mortality for patients with congestive heart failure, but gender and anemia are intimately linked. Survival is impaired by the presence of anemia, with a two-fold increase in mortality for males if present. Finally, anemia plays a small but important role in the incremental risk of patients with heart failure even after adjusting for other important covariates and baseline characteristics including renal function, NYHA class, and medications. The pathophysiologic mechanisms that cause anemia in congestive heart failure have to be determined and therapeutic strategies for the treatment of anemia have to be explored.

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Appendices

Appendix A.

Anemia Is Common in Heart Failure and Is Associated With Poor Outcomes

Insights From a Cohort of 12 065 Patients With New-Onset Heart Failure

Justin A. Ezekowitz, MBBCh; Finlay A. McAlister, MD, MSc; Paul W. Armstrong, MD

Background—Although previous work has suggested that anemia is associated with an increased mortality in selected patients with congestive heart failure (CHF), little is known about the prevalence and predictors of anemia, or whether anemia is an independent prognostic factor in unselected, community-based patients with CHF.

Methods and Results—We analyzed a population-based cohort of patients with new-onset CHF from a database of patients discharged from 138 acute-care hospitals in Alberta, Canada, between April 1993 and March 2001. Logistic regression, Kaplan-Meier survival analyses, and Cox proportional hazards model were used. Among the 12 065 patients with CHF (median age 78 years), 17% had anemia, 58% of whom had anemia of chronic disease. After adjustment for clinical and demographic variables, patients with anemia were more likely to be older (odds ratio [OR] 1.01 per year) and female (OR 1.2 [95% confidence interval 1.1 to 1.3]) and to have a history of chronic renal insufficiency (OR=3.2 [95% confidence interval 2.8 to 3.6]), or hypertension (OR 1.3 [95% confidence interval 1.2 to 1.5]). Hazard ratios for mortality, adjusting for covariates, were 1.34 (1.24 to 1.46) in anemic patients, and 1.36 (1.23 to 1.50) in those patients with anemia of chronic disease.

Conclusions—In this large cohort of community-dwelling patients with CHF, anemia is common and an independent prognostic factor for mortality. Further research into the mechanisms of anemia in CHF and randomized controlled trials to test whether correction of anemia improves prognosis in CHF are needed. **(*Circulation*. 2003;107:223-225.)**

Key Words: anemia ■ heart failure ■ epidemiology

Despite remarkable advances in diagnosis and therapy over the past decade, the prognosis of patients with heart failure remains poor. Identification of factors that adversely affect quality of life or survival in heart failure may not only aid in better definition of prognosis but could also potentially provide new opportunities for novel therapeutic strategies in these patients.

Although anemia (and its correction) is a well-recognized comorbidity in a variety of conditions, including myocardial ischemia, its role in heart failure has only recently received attention.[1–4] Two studies have examined the prevalence and prognosis of anemia in highly selected CHF populations; prevalence was 4% in clinical trial participants (n=6797) with asymptomatic or mild left ventricular dysfunction (relative risk [RR] for death was 1.03 [95% confidence interval (CI) 1.02 to 1.04] for each 1% drop in hematocrit in this sample),[1] whereas 30% of patients (n=1061) followed-up in a specialized clinic for advanced heart failure had anemia (RR 1.13 [95% CI 1.05 to 1.22] for mortality).[2] In a small population-based cohort (n=633) of Medicare beneficiaries admitted to hospital for CHF, 14% had an admission hematocrit <30%, and these anemic patients had increased mortality at 1 year (RR 1.60 [95% CI 1.19 to 2.16]) compared with those with a hematocrit ≥40%.[3] Little is known about the prevalence or prognostic importance of anemia in a large unselected population of patients with heart failure.

Methods

We examined a population-based cohort of 12 065 patients with new-onset heart failure in Alberta, Canada (total population 3.06 million). We used hospital discharge data to identify all patients hospitalized at least once for a most responsible diagnosis of heart failure (International Classification of Diseases [ICD]-9 code 428.x) between April 1993 and March 2001, and collated their comorbidities. The accuracy of our data acquisition and the use of discharge coding to identify cases and comorbidities have been described elsewhere.[5,6] To establish a cohort of incident cases, we excluded patients hospitalized for heart failure in the 12 months preceding the index hospitalization, as well as those who died during the index hospitalization.

We linked the study sample to the Alberta Health Care Insurance Registry, which tracks the vital status of all individuals in the province, and followed-up with all patients from the date of their index hospitalization until the date of their death or September 30, 2001, whichever came first. We determined the prevalence of anemia

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Clinical Features in 12 065 Heart Failure Patients With Any Anemia, Anemia of Chronic Disease, or No Anemia

Characteristic	Any Anemia (n=2083)	Anemia of Chronic Disease (n=1208)	No Anemia (n=9982)
Age, y	77.3±12*	77.3±11*	76.4±12
Male sex	944 (45)*	570 (47)*	4972 (50)
Diabetes	532 (26)	347 (29)*	2346 (24)
Hypertension	738 (35)*	452 (37)*	2829 (28)
COPD	625 (30)	372 (31)	2879 (28)
Hyperlipidemia	78 (4)	58 (5)	349 (4)
Ischemic heart disease	868 (42)*	540 (45)*	3805 (38)
Cerebrovascular disease	107 (5)	58 (5)	393 (4)
Peripheral vascular disease	200 (10)*	117 (10)*	550 (6)
Atrial fibrillation or flutter	548 (26)	313 (26)	2460 (25)
Malignancy	228 (11)*	131 (11)*	536 (5)
Chronic renal insufficiency	387 (19)*	277 (23)*	674 (7)

Values are presented as mean±SD or n (%). Note that the 1208 patients classified as having anemia of chronic disease represent a subset of the 2083 patients with any anemia. COPD indicates chronic obstructive pulmonary disease.

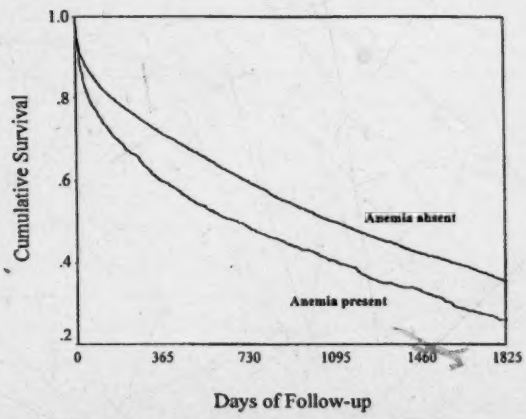
* $P<0.005$ for comparison with no anemia. Statistical significance adjusted for multiple comparisons using the Bonferroni correction.

at the time of initial diagnosis of heart failure (using ICD-9 codes 280 to 289 to capture "all anemia" and 285.9 to capture "anemia of chronic disease") and examined for differences between patients who did and did not have anemia at baseline (Table). Continuous variables were compared using ANOVA adjusted for multiple comparisons by Tukey's test, and ordinal and dichotomous variables were compared using the χ^2 test. Mortality rates of patients who were anemic when heart failure was diagnosed and those without anemia were compared using the Cox proportional hazards model, controlling for comorbidities and the known prognostic factors in heart failure (listed in the Table). Data for regression analysis is presented as odds or hazard ratio with 95% confidence intervals. In a sensitivity analysis to minimize confounding by unmeasured comorbidities, we examined the associations between anemia and outcomes in the youngest and healthiest subgroup (patients <65 years without documented comorbidities).

Results

The median age of our 12 065 patients was 78 years; 17% had anemia (21% iron deficiency, 8% other deficiency, 13% assorted other identifiable causes, and 58% had anemia of chronic disease). Baseline features are outlined in the Table. On multiple logistic regression analysis, anemia was more common in older patients (odds ratio [OR] 1.01 per year, $P=0.002$), women (OR 1.2 [1.1 to 1.3]), patients with chronic renal insufficiency (OR 3.2 [2.8 to 3.6]), or hypertensive patients (OR 1.3 [1.2 to 1.5]).

Median follow-up was 573 days (interquartile range 155 to 1224 days), and the 1-year and 5-year mortality rates were 38% and 59% in those with anemia, respectively, compared with 27% and 50% for those without anemia. The survival of patients with anemia was worse even after adjustment for the known prognostic factors and comorbidities in the Table (Figure). Cox proportional hazard ratios for mortality were 1.34 (1.24 to 1.46) in anemic patients, and 1.36 (1.23 to 1.50) in the subset of patients with anemia of chronic disease. As a sensitivity analysis,



Survival of heart failure patients with and without anemia at the time of initial diagnosis of heart failure. These survival curves were generated using Kaplan-Meier methods ($P<0.0001$ for anemia present versus anemia absent). For results of Cox proportional hazards modeling, please see text.

we restricted this analysis to the youngest and healthiest subgroup (n=654) and found that anemia was even more strongly associated with mortality (OR 2.4 [1.2 to 4.6]).

Discussion

The key novel findings of our study are the demonstration among a large population-based cohort of CHF patients that anemia is common, that it is an independent prognostic factor, and that the majority of heart failure patients with anemia have anemia of chronic disease. There are several possible explanations for our findings. First, reduced hemoglobin may merely be a marker for the epiphenomena of advanced heart failure (such as hemodilution due to volume overload, malnutrition from cardiac cachexia, or renal insufficiency). An earlier study in patients with New York Heart Association class III or IV failure demonstrated, however, that hemoglobin was an important prognostic factor independent of the pulmonary capillary wedge pressure, body mass index, serum albumin, or serum creatinine.[2] Furthermore, anemia was an independent predictor of mortality independent of serum creatinine in 2 previous studies.[1,3] Second, because angiotensin-converting enzyme (ACE) inhibitors may inhibit hematopoietic cell proliferation, it is possible that anemia may be a marker for patients receiving higher doses of ACE inhibitors.[7,8] This seems unlikely, however, as the presence of anemia seems to be independent of ACE inhibitor use (and dosing).[1,2] Third, although anemia may predispose at-risk patients to myocardial ischemia, the prognostic impact of anemia was independent of a diagnosis of ischemic heart disease in our data. Finally, inflammation, characterized by increases in cytokines such as tumor necrosis factor-α,[9] is now thought to be a pathophysiological modulator of heart failure. Hence, we believe it is reasonable to hypothesize that heart failure may cause anemia of chronic disease through cytokine-mediated bone marrow suppression.[7]

As this is an observational study, some potential limitations deserve discussion. The limitations of administrative data-

bases are well known and described elsewhere.[5] However, previous studies have confirmed the accuracy of our data sources and coding for heart failure.[5,6] Further, all of our analyses were adjusted for known prognostic factors in heart failure, and we confirmed the robustness of our findings in a sensitivity analysis in the youngest and healthiest subgroup, where unmeasured confounding would presumably be minimized.[10]

We believe efforts to better detect anemia in heart failure patients, discern the pathophysiology of, and test new therapies for anemia in heart failure should be a future priority. Indeed, small open-label studies have shown improvements in functional capacity and ejection fraction with correction of anemia using erythropoietin with intravenous iron.[4,11] There is clearly a need for an appropriately powered randomized trial with meaningful clinical endpoints, such as hospitalizations and mortality, to evaluate the impact of such therapies in anemic heart failure patients.

Acknowledgments

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Appendix B.

HEART FUNCTION CLINIC – PATIENT STATUS SUMMARY

Clinic Date: May 2. 2003

Etiology of HF:
Secondary diagnoses:

Medication	Changed By	Reason

SYMPTOMS						
Exercise	**Fatigue Level**	**Exertional Dyspnea**	**Angina**	**Orthopnea**	**Swelling**	**Compared to last visit**
	o Better o Same o Worse	o Better o Same o Worse	o Better o Same o Worse o N/A	#Pillows oPND oPalpitation oLight head	o Leg o Abdo o GI Comp oEx Diuretic	o Better o Same o Worse o Clinic stable o Admitted
Comments:						

ASSESSMENT										
Weight	**BP**	**HR**	**JVP**	**Peripheral Edema**	**Heart Sounds**	**Chest**	**SOB**	**Fatigue**	**NYHA**	**CCS**
Clinic Home	Sit Stand			o 0 o +1 o +2 o +3	o Mitral o Aortic o Other o S_3 o S_4	o Clear o Crackle o Wheeze	Ex Rest	Ex Rest	o I o II o III o IV	o I o II o III o IV o N/A
Comments:										

CURRENT LAB RESULTS	**INVESTIGATIONS /INTERVENTIONS**	**HOSPITALIZATIONS** (dates, dx, site)

IMPRESSION & PLAN			
	Action	Investigations	Education
	o Change in meds o Clinic Trial	o CXR o Echo o ECG o Blood Wk. o Other	o Disease o Meds o Fluid/Salt o Monitor Wt. o Exercise

Next Visit: _____

HEART FUNCTION CLINIC PATIENT PROFILE

Name _____ ☐ M ☐ F DOB _____ Age_____ Tel.#: (H)_____ (B)_____ PHN#_____ UAH#_____ Race: ☐ Caucasian ☐ Aboriginal ☐ Asian ☐ Black ☐ Other_____	Patient Label

REFERRAL INFORMATION

Date received:_____
Referred by: Dr._____
MD type: ☐ Card. ☐ GP ☐ Int. ☐ Other_____
Location: ☐ Hosp. _____ ☐ Clinic _____ Approved:_____
Tests ordered prior to initial appt_____:

- ☐ Lab _____
- ☐ Echo _____
- ☐ CXR _____
- ☐ ECG _____
- ☐ Other:_____

CHF

Etiology of CHF:_____
Onset of CHF:_____
Last episode of CHF:_____ Hospitalized?: ☐ No ☐ Yes- site_____
Dysfunction: ☐ Systolic ☐ Diastolic ☐ Combined
EF: _____% by _____
NYHA Functional Class: ☐ 1 ☐ 2 ☐ 3 ☐ 4

CCHFCN

Co-Morbidity

- ☐ COPD
  - Smoking
    - ☐ non-smoker
    - ☐ ex-smoker- quit _____
    - ☐ current _____
- ☐ History of CAD
  - ☐ PTCA
  - ☐ Stent
  - ☐ CABG
- ☐ Valve Disease
- ☐ HTN
- ☐ Dyslipidemia
- ☐ Diabetes- Type_____ controlled with ☐ diet & exercise ☐ OHA ☐ insulin ☐ OHA & insulin
- ☐ PVD
- ☐ Cerebral Vascular Disease- ☐ TIA _____ ☐ CVA (R / L)_____
- ☐ Morbid Obesity (BMI>35)
- ☐ Renal insufficiency
- ☐ Liver disease
- ☐ Cancer
- ☐ Gout
- ☐ Arthritis
- ☐ Depression
- ☐ ETOH abuse
- ☐ Drug abuse
- ☐ HIV
- ☐ Other _____

Dysrhythmias

- ☐ Atrial flutter
- ☐ Atrial fibrillation
- ☐ SVT
- ☐ Ventricular tachycardia
- ☐ Ventricular fibrillation
- ☐ Bradyarrhythmias
- ☐ Rx_____

Pacemaker

Date_____
Type_____
Settings_____
_____
Reason_____
Pacemaker Clinic_____

Appendix C.

Appendix D.

Table 9. Comparison of Patients with and without a Hemoglobin in the Database

	Hemoglobin present (n=791)	Hemoglobin absent (n=246)	P
Female (%)	35	33	0.596
Ischemic history (%)	61	67	0.600
Systolic dysfunction (%)	29	24	0.175
NYHA Class II/III	79	74	0.114
Age (years)	67 (14)	63 (14)	0.010
Ejection Fraction (%)	33 (15)	33 (15)	0.492
Died in Follow-up (%)	288 (39)	84 (34)	0.300

NYHA = New York Heart Association. Ejection fraction and age are expressed as mean (standard deviation). P value represents comparison between hemoglobin present/absent by either Chi-square or ANOVA.

Appendix E.

Table 10. Univariate Predictors of 1-Year Mortality (Logistic Regression) and Mortality Throughout Entire Follow-up Period (Cox Regression).

	1-year Mortality			Overall Mortality		
Variable	**p-value**	**Odds Ratio**	**95%CI**	**p-value**	**HR**	**95%CI**
Demographic						
Age	0.015	1.01	1.00 to 1.02	<0.001	1.03	1.02 to 1.04
Female	0.083	0.77	0.57 to 1.04	0.036	0.75	0.57 to 0.98
Cardiovascular History						
NYHA Class III/IV	<0.001	1.89	1.42 to 2.51	<0.001	2.00	1.55 to 2.59
Ischemic Etiology	0.466	0.89	0.68 to 1.19	<0.001	1.76	1.34 to 2.32
Hypertension	0.474	0.90	0.68 to 1.20	0.162	0.83	0.63 to 1.08
Systolic Dysfunction	0.051	0.74	0.55 to 1.00	0.001	1.61	1.20 to 2.16
Ejection Fraction >50%	0.494	0.87	0.59 to 1.29	0.338	0.84	0.59 to 1.20
Ejection Fraction	0.566	1.00	0.99 to 1.01	0.488	1.01	0.99 to 1.02
Ventricular arrhythmias	0.325	0.84	0.58 to 1.20	0.041	1.39	1.01 to 1.90
Atrial arrhythmias	0.527	1.10	0.82 to 1.48	0.200	1.19	0.91 to 1.57
Pacemaker	0.722	1.10	0.64 to 1.92	0.531	0.85	0.49 to 1.43
COPD	<0.001	2.70	1.80 to 4.04	0.715	1.08	0.72 to 1.62
Diabetes Mellitus	0.049	1.36	1.00 to 1.86	0.336	1.15	0.86 to 1.54
Dyslipidemia	0.004	1.84	1.21 to 2.79	0.001	0.47	0.29 to 0.75
Physical Examination						
Weight	0.094	0.99	0.98 to 1.00	0.003	0.99	0.98 to 1.00
Heart Rate	0.668	1.00	0.99 to 1.01	0.889	1.00	0.99 to 1.01
Systolic BP	0.023	0.99	0.98 to 1.00	0.003	0.99	0.99 to 1.00
Diastolic BP	<0.001	0.97	0.95 to 0.98	<0.001	0.97	0.96 to 0.98
Edema Present	0.004	1.57	1.16 to 2.13	0.007	1.48	1.11 to 1.98
LBBB	<0.001	0.49	0.35 to 0.68	<0.001	1.68	1.28 to 2.22
LVH	<0.001	0.48	0.34 to 0.66	0.805	0.97	0.73 to 1.27
Medications						
ACE inhibitors	<0.001	0.32	0.22 to 0.45	0.090	0.75	0.53 to 1.05
ARB	0.131	0.57	0.27 to 1.18	0.042	0.51	0.26 to 0.99
Beta-Blockers	<0.001	0.48	0.36 to 0.64	<0.001	0.38	0.29 to 0.49
CCB DHP	0.003	0.52	0.34 to 0.81	0.003	0.57	0.40 to 0.84
CCB Non-DHP	0.096	0.63	0.36 to 1.09	0.204	1.33	0.86 to 2.07
Warfarin	0.014	0.70	0.53 to 0.93	0.478	1.09	0.85 to 1.41
Aspirin	<0.001	0.52	0.39 to 0.68	0.586	1.08	0.82 to 1.41
Digoxin	0.007	0.68	0.51 to 0.89	0.014	1.40	1.07 to 1.83
Spironolactone	0.082	1.41	0.96 to 2.08	<0.001	0.04	0.02 to 0.11
Loop diuretics	0.010	0.63	0.45 to 0.90	0.012	1.57	1.10 to 2.25
Amiodarone	0.049	0.64	0.42 to 1.00	0.002	1.75	1.22 to 2.50
Vasodilator	0.039	0.61	0.38 to 0.97	<0.001	0.23	0.13 to 0.39
Laboratory Values						
Creatinine Clearance	0.001	0.99	0.98 to 1.00	<0.001	0.98	0.98 to 0.99
Sodium	0.576	0.99	0.95 to 1.03	0.115	0.98	0.94 to 1.00
Hemoglobin	0.023	0.99	0.98 to 1.00	0.001	0.99	0.98 to 1.00

COPD = Chronic obstructive airways disease; CCB = Calcium Channel Blockers; DHP = Dihydropyridine; NYHA = New York Heart Association Class; BP = Blood Pressure; HR= Hazard Ratio; 95%CI = 95% Confidence Interval